

Thesis for the degree of Candidatus Pharmaciae

**APPLICATION OF ONE-POT SYNTHESIS OF Cu(I)-
CATALYZED CYCLOADDITION BETWEEN AZIDES AND
TERMINAL ALKYNES:
A NEW ONE-POT SYNTHESIS OF 1,4-DISUBSTITUTED 1,2,3-
TRIAZOLES FROM TERMINAL ACETYLENES AND *IN SITU*
GENERATED AZIDES**



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Abstract

Multi-component reactions are a very elegant and rapid way to access highly functional molecules from simple building blocks in drug lead synthesis. Multi-component one-pot reactions generally afford good yields which is important in combinatorial synthesis.

Over the past decade, several sequential multi-component reactions have been developed into multi-component one-pot reactions. Since multi-component one-pot reactions results in a reduced number of operations, they usually allows direct transformation of intermediates to desired products by avoiding isolation, handling and chromatography. Hence, better yields are usually achieved.

In this study 1,4-disubstituted 1,2,3-triazoles were obtained by a high-yielding copper (I) catalyzed 1,3-dipolar cycloaddition reaction between in situ generated azides and terminal acetylenes. This one-pot, two-step procedure tolerated most functional groups and circumvented the problems associated with the isolation of potentially toxic and explosive organic azides. All of these factors are important in combinatorial synthesis of drug lead compounds.

Abbreviations

^{13}C NMR	Carbon nuclear magnetic resonance
CDCl_3	Deuterated chloroform
DMSO	Deuterated methylsulfoxid
EtOAc	Ethylacetate
EtOH	Ethanol
GTP	Guanosine 5-triphosphate
H	Hydrogen
^1H NMR	Hydrogen nuclear resonance
HRMS	High resolution mass spectrometry
HTS	High throughput screening
Hz	Hertz
<i>J</i>	Coupling constant
MeOH	Methanol
Mp	Meltingpoint
$[\text{M}^+]$	Molecular ion
NaAscorbate	Sodium ascorbate
PABA	Para-aminobenzoic acid
R_f	Retention factor
t-BuOH	tert-buthanol
TLC	Thin layer chromatography
α	Alfa
β	Beta
d	Doublet
q	Quartet
s	Singlet
t	Triplet

Table of contents

ACKNOWLEDGEMENTS.....	2
Abstract.....	3
Abbreviations.....	4
Table of contents.....	5
1. Drug development.....	6
1.1 Introduction.....	6
1.2 Combinatorial chemistry:.....	7
1.3 High throughput screening.....	9
1.4 Click chemistry	10
1.5 Synthesis of starting compounds	15
1.6 Tubulin and tubulin inhibitors	18
1.7 Sulfonamides.....	20
1.8 Aim of study	22
2. Results and Discussion	23
2.1 Syntheses.....	23
2.1.1 Syntheses of alkynes.....	23
2.1.2 Syntheses of azides.	30
2.1.3 Desalting of 3-(bromomethyl-)pyridine hydrobromide	32
2.1.4 Syntheses of bromides	33
2.2 Click reactions	35
2.2.1 One pot syntheses	35
2.2.2 1,4 Disubstituted cyclo additions.....	43
3. Experimental.....	47
3.1 General procedures	47
3.2 Synthesis	49
4 Further studies and conclusion.....	72
4.1 Further studies.....	72
4.2 Conclusion	73
5. References.....	74

1. Drug development

1.1 Introduction

Even though we have come a long way in discovering drugs in many areas of human diseases, there is still a great demand for new and better drugs. New illnesses come along that need new drugs to combat them, and drugs that were once efficient are now futile against many common diseases. This might, for example, be due to resistance among bacteria. Other reasons to develop new drugs can be that the synthesis of the existing drug is difficult, expensive or harmful to the environment. Some drugs also have unacceptable side effects to go along with their wanted effects. Side effects might be minimized by altering the molecule slightly.

Pharmaceutical companies and academic milieus are constantly putting in a great effort to discover new pharmaceutical compounds. This is a very laborious task, which in many cases is done practically “blindfolded” in a trail and error manner. This means that one needs a vast amount of compounds.

A typical new pharmaceutical compound costs in the area of \$800 mill. to develop from idea to a product ready for marketing (2001).¹ Any enhancement in any step of the development of novel drugs would be of great value to any pharmaceutical company. If there is a way to avoid one step in the synthesis and purification process, a lot of money would be saved. This is why a synthetic reaction that is facile and high yielding would be suitable for preparing a vast amount of new compounds. To screen a large number of new compounds for possible effects one would need a tremendously large number of workers or a smart method. High throughput screening (HTS) allows you to investigate thousands of compounds each day. The principles of HTS will be further discussed later.

1.2 Combinatorial chemistry:

All of the 10 largest selling drugs in 1994 were small organic molecules, i.e., compounds with molecular weights less than 700 daltons.² Due to this fact, much of the efforts of drug discovery are focused on small, organic molecules. To synthesize a reasonable library of compounds it is important to synthesize a great number of them. The traditional methods of organic chemistry limits chemists productivity a lot. A way to solve this problem is to do multiple reactions simultaneously. To do multiple reactions at the same time there are two key challenges that has to be met. First you have to develop reactions that are reliable and constantly produce satisfactory yields. The reactions should also be compatible with a large number of starting materials. Once you have found your preferred reactions, you need to develop a method to efficiently detect and identify your products.

And the generation of molecular diversity by chemical synthesis is also important in drug discovery. The generation of molecular diversity is also based on the concepts of peptide synthesis. It was first reported by Merrifield³ in 1963 that it was possible to obtain good yields and simple isolation techniques by using polymeric supports for the synthesis of peptides.

Simultaneous synthesis of many products at the same time in multiple reaction vessels, often on a plate, is known as parallel synthesis. The concept is to mix and react two different groups of molecules, for example amines and carboxylic acids. For simplicity, let us consider a plate that has 4x4 wells. We have 4 amines: A1-A4 and 4 carboxylic acids: B1-B4. Each amine goes in a horizontal row. And each carboxylic acid goes in a vertical row. (See Figure 1) As seen in fig.1, we end up with a total of 16 products.

A1B1	A1B2	A1B3	A1B4
A2B1	A2B2	A2B3	A2B4
A3B1	A3B2	A3B3	A3B4
A4B1	A4B2	A4B3	A4B4

Figure 1: Parallel synthesis

In combinatorial synthesis one perform multiple reactions in the same vessel. An example of the simplest way to perform a combinatorial synthesis is one vessel filled with multiple reactants. If we mix two acids and five amines in a vessel to perform an amide reaction, we would end up with $2 \times 5 = 10$ products.. An advance in combinatorial chemistry came with the portion-mixing approach described by Furka in 1988⁴. This method is known as the split and mix method. Using this method, we mix the two acids and divide the mixture into five vessels where we add the five different amines into each one. We produce a library of compounds that exist in several mixtures. These mixtures are suitable for analysis with assays. The split and mix method can be utilized to make vast compound libraries in a short period of time.

In the two techniques described above it is common to attach the reactants to a solid phase. The solid phase can be beads made of polymeric material. This eases the process of isolation as well as giving higher yields, and also renders purification unnecessary.

1.3 High throughput screening

To be able to analyze the enormous number of compounds obtained by using combinatorial chemistry, a powerful method is needed. A HTS system is built around a plate with small wells, where samples and assay reagents are deposited. The aim of the assays is to detect “hits”. A “hit” is a positive result. There can be a variety of detector systems. They can detect radioactivity, luminescence or fluorescence for example. Detection of such signals indicates a “hit”, and the strength of them indicate the quality of the “hit”. MS detection is also used to identify products, even on single beads taken from a sample.⁵ If a “hit” is detected, the chemist has to look closer at the compounds in the well that produced the “hit”.

A HTS system is often set up to be automated. The use of robotics is both time and cost effective. The chemists’ job is to find the appropriate assay to the library compounds and program the robotics to deliver the needed samples to the wells on the plate.

1.4 Click chemistry

Professor K. B. Sharpless and co-workers at The Scripps Research Institute in 2001 introduced click chemistry as guiding principles for organic synthesis. Click chemistry was their response to the problems associated with making reliable libraries of potential lead structures using combinatorial chemistry. Click chemistry is a modular approach to chemical synthesis that utilizes only the most practical and reliable chemical transformations.

To fit into the category of click chemistry a reaction has to meet certain requirements.^{6,7}

- 1: It has to be a facile and selective reaction.
- 2: It must be of a wide scope, meaning that it will provide high yields from a large variety of starting compounds consistently.
- 3: It must be easy to perform and insensitive to water and oxygen.
- 4: It must use only readily available reagents.
- 5: The reaction has to be easy to work up and the product isolation must be simple, without requiring any chromatography.

Its applications are increasingly found in all aspects of drug discovery, ranging from lead finding of new drug candidates through proteomics as well as DNA research utilizing bioconjugation reactions.

Despite many successes, drug discovery approaches that are based on Nature's secondary metabolites, *i.e.* natural products, are often hampered by slow and complex synthesis of drug candidates. Through the use of only the most facile and selective chemical transformations, click chemistry simplifies synthesis and purification in medicinal chemistry based on natural products. This will enable faster discovery of lead molecules, as well as speed up the optimization of existing biologically active compounds that targets a specific receptor. Thus, click chemistry is a set of powerful, virtually 100%

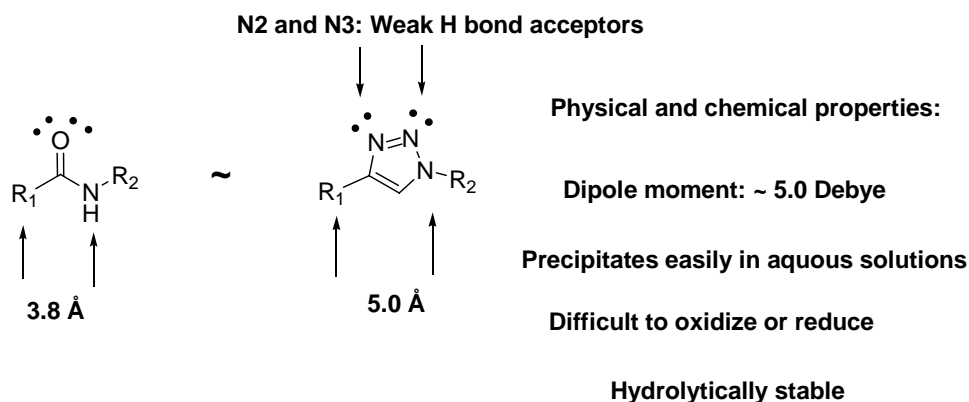
reliable, selective reactions for rapid synthesis of a wide variety of biologically active compounds.

Click chemistry uses carbon-heteroatom bond-forming connection chemistry.⁶ In click chemistry the focus is on highly energetic reactants and kinetic control of the reaction, hence click chemistry reactions are also irreversible.

Click reactions utilize benign reaction conditions. They should work very well in water and in the presence of oxygen. This is a great advantage because it limits the use of environmentally unfriendly solvents used in “traditional” chemical synthesis. The fact that the reactions are insensitive to oxygen makes them a whole lot easier to perform. There is no need to do them under argon or nitrogen. This limits the effort required. A huge advantage of click chemistry is that they use strongly driven and highly selective reactions. The reactions are run at neutral pH or slightly alkaline pH.

Another benefit is that the triazole ring is not just a passive link, it interacts with biological targets through hydrogen bonding and dipole interactions.⁶ Many pharmaceutical compounds include heterocycles as a functional group. Click chemistry gives access to a vast variety of five and six membered heterocycles through such reactions as hetero Diels-Alder and 1,3-dipolar cycloadditions⁸.

The 1,4-disubstituted 1,2,3-triazoles prepared by a copper-(I)-catalyzed reaction between terminal alkynes and azides (Figure 2),⁹ is an example of a synthesis that produces one of the heterocycles mentioned above. This reaction seems well suited for medicinal chemistry for the rapid development of drug lead compounds. The regioisomeric product formed, the 1,4-disubstituted 1,2,3-triazole, shares topological and electronic features with Nature’s ubiquitous amide connectors. Unlike amides, triazoles are not susceptible to cleavage and are hence stable both *in vitro* and *in vivo*.



1,4-Disubstituted 1,2,3-triazoles could serve as amide linkers

Figure 2: Amides and 1,2,3-triazoles share topological and electronic features

Given the readily access to the starting azides and terminal alkynes, highly diverse and unambiguous lead compounds should become available quickly, since there are no need for protection and deprotection steps under click chemistry conditions. Furthermore, with complete conversion of starting materials and with exclusive selectivity for the 1,4-disubstituted 1,2,3-triazoles, the process of identification and discovery of new drug lead compounds, as well as optimization of existing ones, should become more efficient.

Because click chemistry relies on a small number of near perfect reactions there is some concern that there will be limits to the potential chemical diversity of the compound libraries obtained by using the procedures. In a computational study by Guida *et al.* it is suggested that the number of drug like compounds are as large as 10^{63} .¹⁰ A drug like compound has less than 30 non H-atoms, a size less than 500 daltons and includes only H, C, N, O, P, S, F, Cl and Br and they must be likely to be stable in presence of water and oxygen. At this point somewhere between 10^6 and 10^7 such molecules are known. This means that only a very small part of the potential drugs have been discovered. Click chemistry can't explore all of these possibilities, but it is a fast and effective way to explore a huge number of interesting molecules that can be made with relative ease. In this way research can focus on the part of the 10^{63} different molecules that are easy to make and isolate rather than starting with the ones that requires complex synthesis.

The Huisgen 1,3-dipolar cycloadditions of azides and alkynes to give triazoles, is a useful cycloaddition reaction that gives heterocycles.¹¹ Even though the reaction is favored kinetically, it may require elevated temperature and it usually results in a mixture of the 1,4 and 1,5 regioisomers.

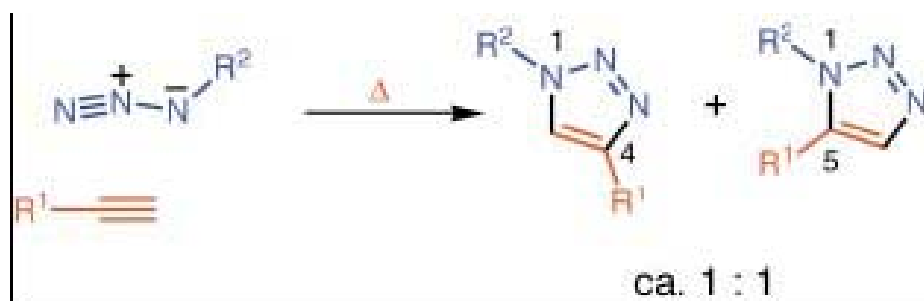


Figure 3: Regioisomers of 1,2,3-triazoles¹¹(Reprinted)

Efforts to control this 1,4- versus 1,5 regioselectivity problem was met with various success until the copper(I)-catalyzed reaction was discovered.¹¹ While a number of copper(I) sources can be used, it was found that the catalyst was better prepared in situ by reduction of copper(II) salts. Copper sulphate serves well as a source. As the reductant, ascorbic acid or sodium ascorbate proved to be excellent. With 0.25-2% mol of the copper(I) catalyst the reaction is regiospecific at ambient temperatures and yields only the 1,4-disubstituted 1,2,3-triazoles.¹¹

The mechanism proposed by Rostovtsev *et al.* is shown in Figure 4. It starts with the formation of the copper (I) acetylide. Functional theory calculations and experimental work published by Sharpless *et al.* in 2005¹² points to a stepwise, annealing sequence rather than the concerted [2+3] cycloaddition.

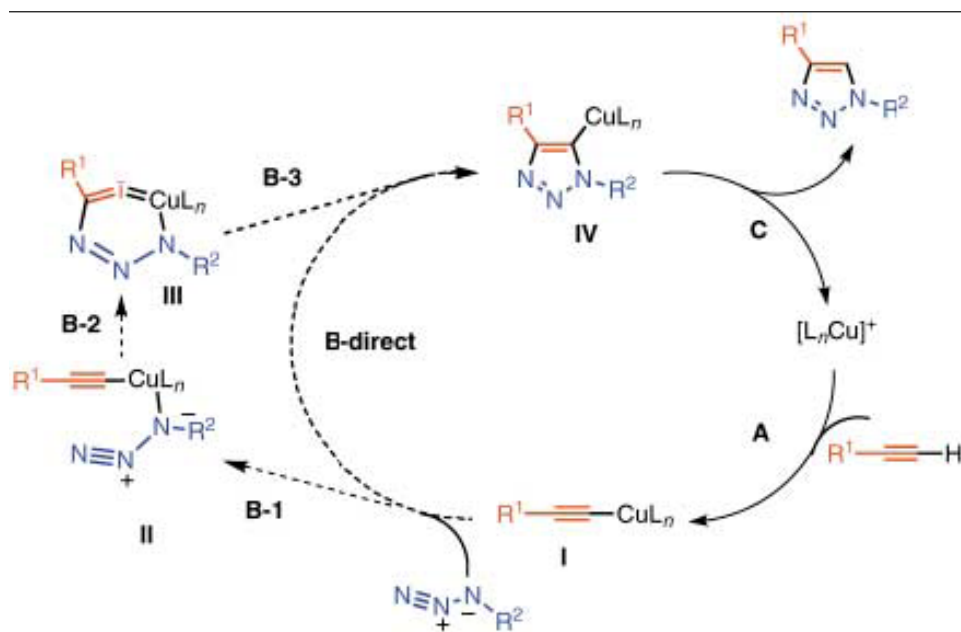


Figure 4: Mechanism of copper(I) catalysis. Reprinted¹¹

1.5 Synthesis of starting compounds

Terminal alkynes can be synthesized in numerous ways. Some common procedures will be outlined here.

McKelvie reported the synthesis of 1,1-dibromoolefins (ylide) via phosphine-dibromomethylenes in 1962.¹³ (Figure 5) This discovery was important for future work.

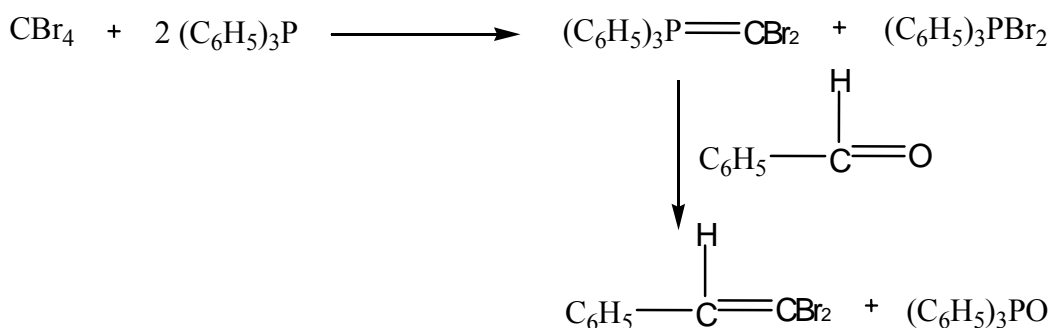


Figure 5: A 1,1-dibromoolefin

In 1972 Corey and Fuchs synthesized terminal alkynes from aldehydes.¹⁴ The synthesis involves 2 steps. (Figure 6) Notice that the first step is the same as in Figure 5.

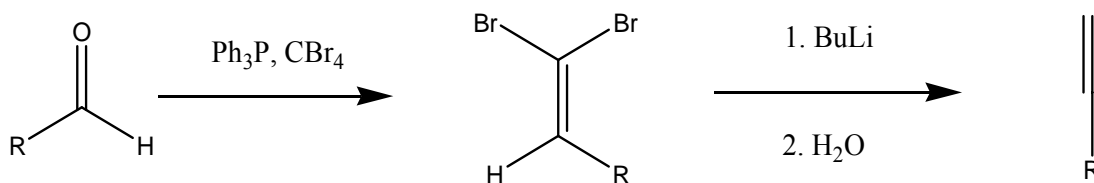


Figure 6: Corey-Fuchs synthesis of terminal alkynes

Colvin and Hamill reported a one-step conversion of carbonyl compounds into acetylenes in 1973.¹⁵ (Figure 7)

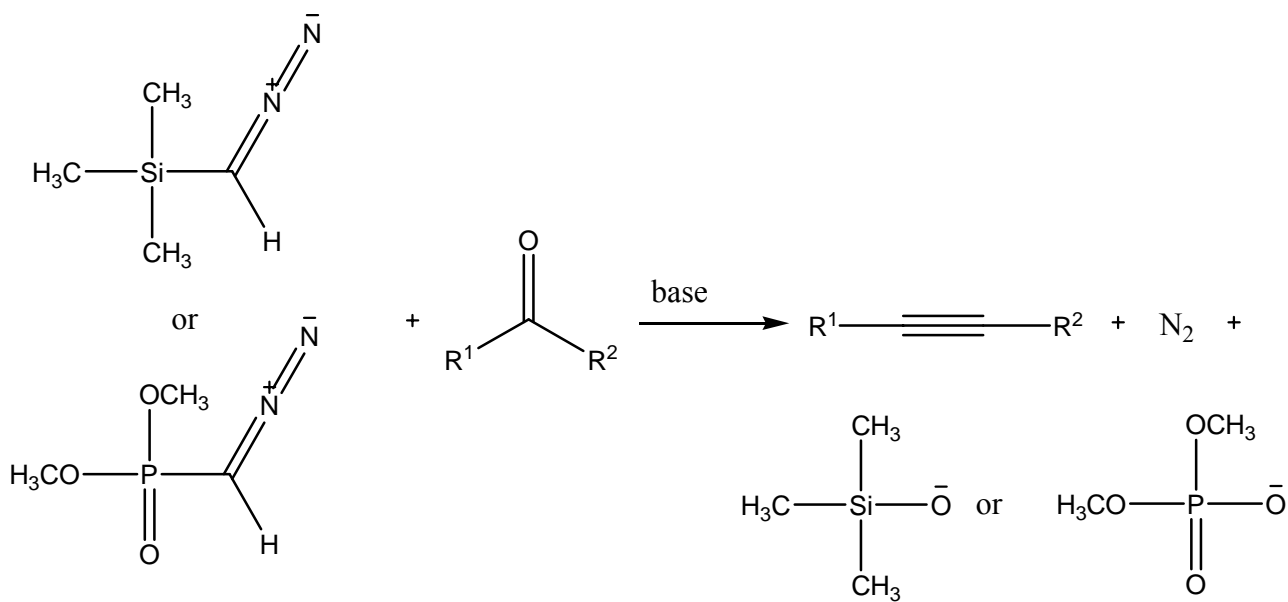


Figure 7: Colvin and Hamill conversion.

Ohira reported a useful means of preparing dimethyl (diazomethyl)-phosphonate.¹⁶ (Figure 8)

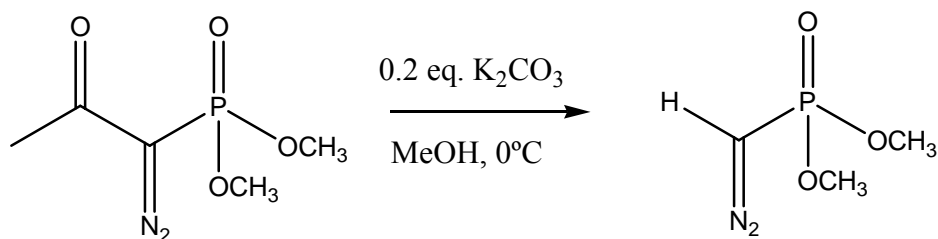


Figure 8

Bestmann reported a one pot procedure for preparing terminal alkynes with the reagent dimethyl-1-diazo-2-oxopropylphosphonate.¹⁷ (Figure 9)

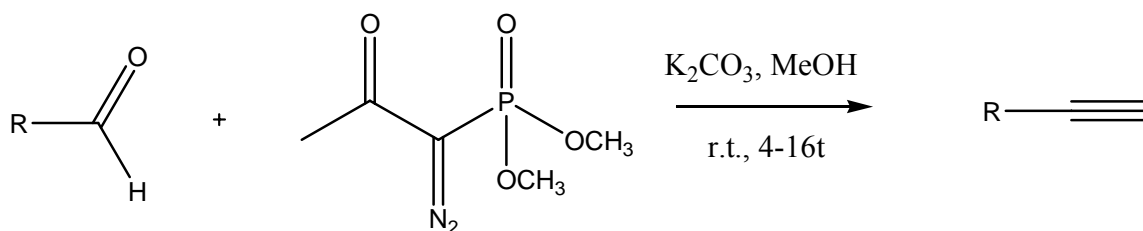


Figure 9

Azides are readily accessible through numerous reactions. One way to obtain azides are nucleophilic substitution reactions. ($\text{S}_{\text{N}}2$ type.) These and other ways to obtain azides are thoroughly reviewed in “Organic Azides: An Exploding Diversity of a Unique Class of Compounds”.¹⁸

1.6 Tubulin and tubulin inhibitors

Every nucleated cell in the human body contains two similar spherical proteins called α and β tubulin. These two come together to form an α - β heterodimer. These heterodimers can, in the presence of GTP at 37°C, form long protein fibers called protofilaments. These protofilaments group together and curl up to form pipe-like structures called microtubules.¹⁹ The microtubules give the cell support, acting like a scaffold. They also organize the organelles of the cell. The most important role of the microtubules is the formation of the mitotic spindle. The mitotic spindle is involved in the cell replication process, where it “pulls” the chromosomes towards opposite sides of the dividing cell. (Figure 10)

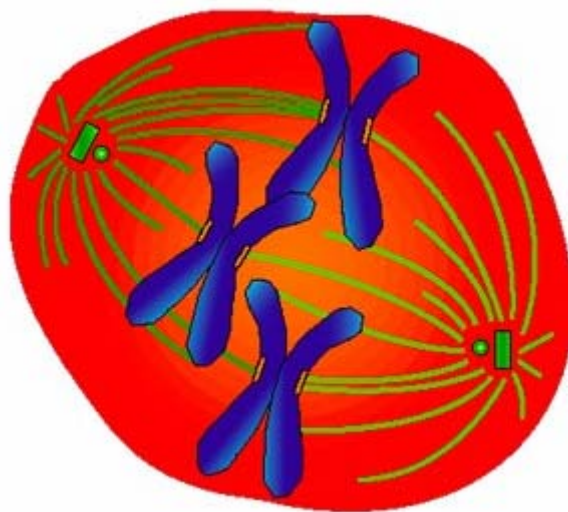


Figure 10: Microtubules in mitosis. Reprinted²⁰

In cancer cells the cell replication process is out of control.¹⁹ One target for controlling the growth of a tumor is therefore to inhibit the formation of microtubules. There are separate classes of drugs that bind to tubulin. All tubulin inhibiting substances are divided

fit into classes depending upon the effect which that substance exerts on the binding site of five characterized tubulin agents to tubulin. These agents are colchicine, vincristine, vinblastine, rhizoxin and myatansine.¹⁹

Combretastatin A-4(Figure 11) is isolated from the South African Willow, *Combretum caffrum*, and has a simple chemical structure that shows antimitotic effect by interaction with the colchicine binding site on tubulin.²¹ Combretastatin A-4 has shown an impressive spectrum of activity, including inhibition of angiogenesis, which is essential for tumor growth.²² Combretastatin A-4 has been considered for clinical trials, but these met an obstacle due to the poor water solubility of the drug. There is currently being done a lot of research to make analogues that overcome this problem.

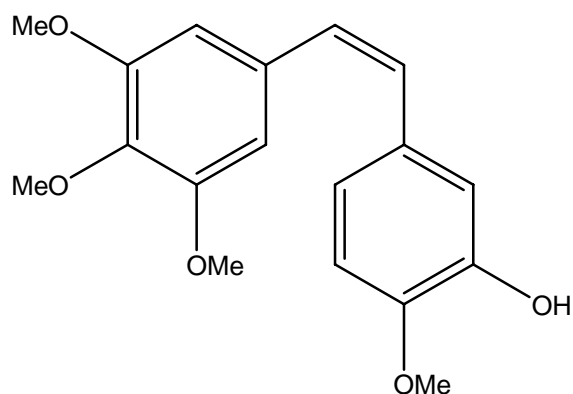


Figure 11: Combretastatin A-4

1.7 Sulfonamides

In the early 1930s Gerhard Domagk tested a variety of azo dyes for antibacterial activity. Prontosil showed significant results in test. The dye successfully protected mice against streptococcal infections.²³ Later Tréfouël found that prontosil was not active in vitro, but when a reducing agent was added the drug was active.²⁴ It was found that prontosil needed to be reduced to sulfanilamide to be active. The discovery of prontosil, and its properties, marks the beginning of modern chemotherapy and structure-activity relationship studies.

A breakthrough in the discovery of the mechanism of action for the sulfonamides was made in 1940 by Woods.²⁵ He showed that the *p*-aminobenzoic acid was a potent inhibitor of sulfanilamide induced bacteriostasis in streptococcal infected mice. Finally, Miller demonstrated that sulfanilamide inhibited the folic acid biosynthesis, that is critical for the growth of bacteria.²⁶

A major concern with the use of sulfonamide drugs is the development of drug resistance. One mechanism of drug resistance is that the bacteria develop an enzyme that is less sensitive to sulfonamides than *p*-aminobenzoic acid.²⁷ Another mechanism involves altered permeability to the sulfonamides.²⁸ Synthesis of analogues that avoid these problems could prove very valuable.

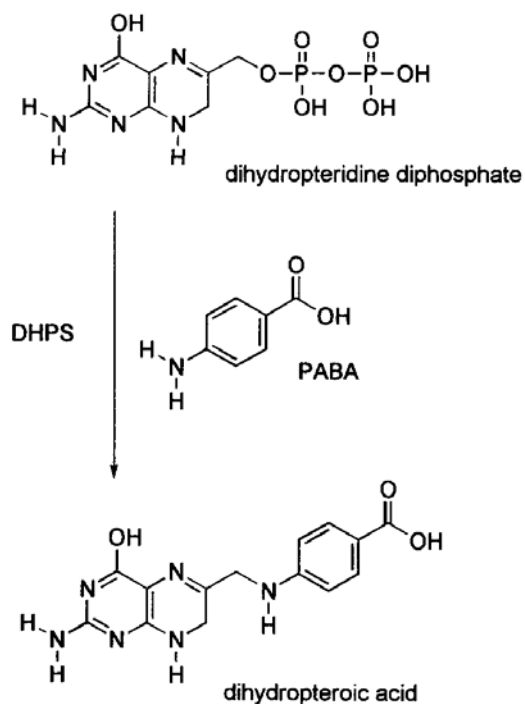


Figure 12: Biochemical reaction catalyzed by dihydropteroic synthetase²⁹ (reprinted).

Biochemical synthesis of dihydropteroic acid is shown in Figure 12. The various sulfonamide analogs inhibit this synthetic pathway by competitive inhibition of PABA. The sulfonamides have a similar structure to PABA and therefore they can interfere in the reaction shown in Figure 12. Dihydropteroic acid is essential to the formation of folic acid that is required as precursors in the synthesis of both DNA and RNA in bacteria and mammals.

1.8 Aim of study

In the present study it is sought to synthesize 1,2,3-triazole analogues of combretastatins and antibacterial sulfonamides. In addition, another aim was to see if new one-pot click chemistry procedures could be developed.

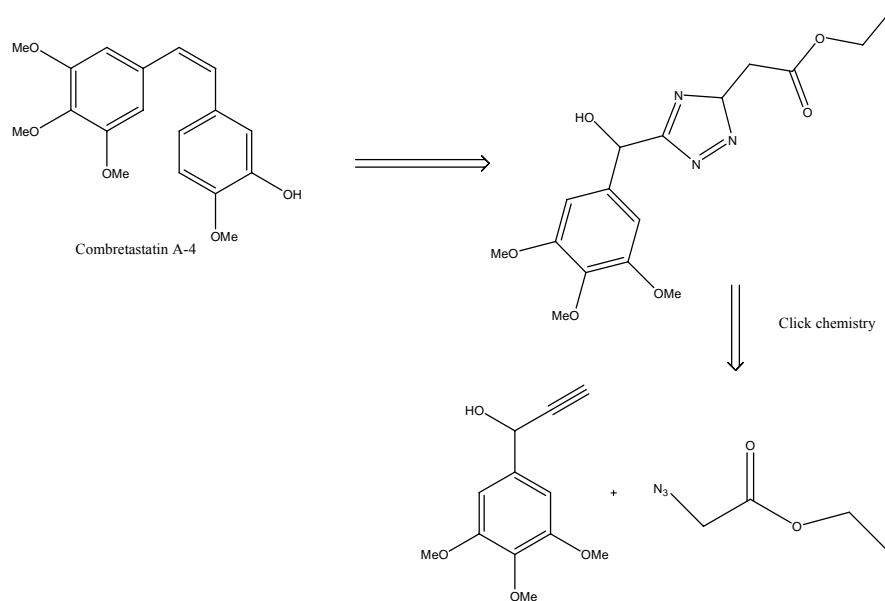


Figure 13: Example of synthesis of a combretastatin analogue

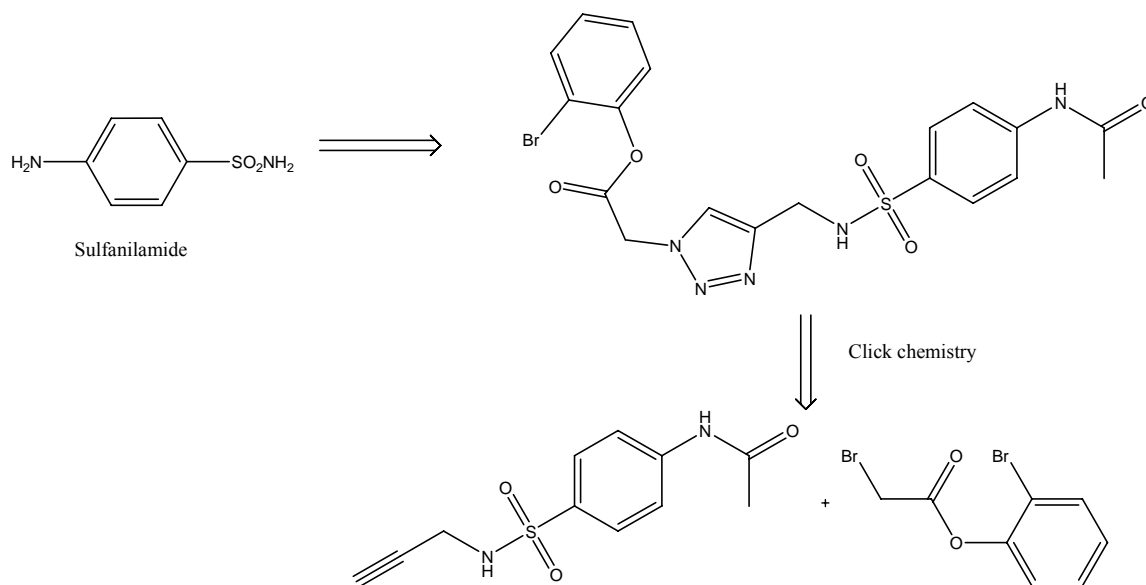


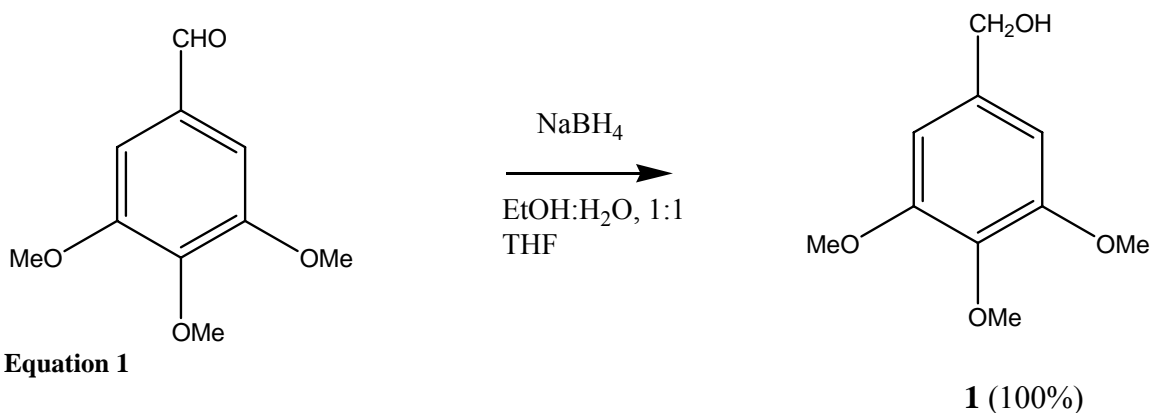
Figure 14: Example of synthesis of a sulfanilamide analogue

2. Results and Discussion

2.1 Syntheses

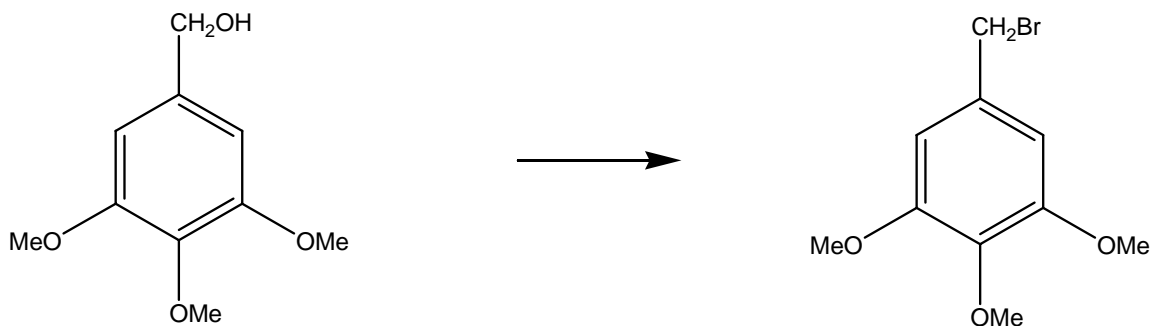
2.1.1 Syntheses of alkynes

The first object of the study was to synthesize the starting materials. To obtain alkynes a reduction from 3,4,5-trimethoxybenzaldehyde to (3,4,5-trimethoxyphenyl)methanol (**1**) was performed, as outlined in Equation 1.



The product had a R_f in hexane:EtOAc (2:1) of 0.13. ^1H NMR spectra of the product showed a singlet at 6.58 ppm with an integral height of 2 that indicated two aromatic protons. A singlet at 4.62 ppm with an integral height of 2 indicated two protons in α -position to a benzene ring. Two singlets at 3.85 ppm and 3.82 ppm with integral heights of 6 and 3 indicated nine methyl protons. There was no signal for the proton on the alcohol group. ^{13}C NMR data showed a peak at 153.30 ppm that indicated two aromatic carbons. Two peaks at 137.23 ppm and 136.63 ppm representing two aromatic carbons. At 103.75 a peak represented two aromatic carbons. A peak at 65.43 ppm indicates an aliphatic carbon. At 60.80 ppm and 56.03 ppm two peaks for the three methyl carbons were shown.

The product **1** was used to synthesize 5-(bromomethyl)-1,2,3-trimethoxybenzene (**2**), as shown in Equation 2

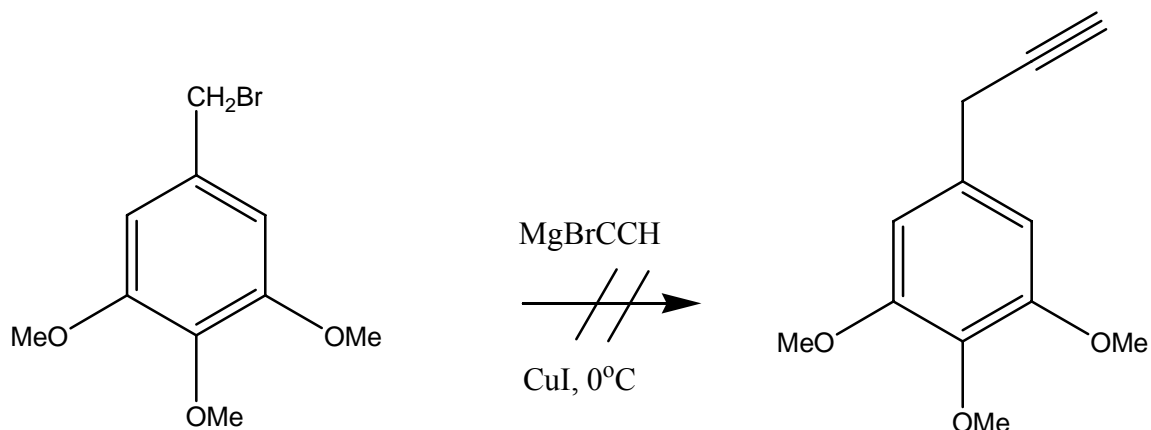


Equation 2

2 (58%)

The melting point of **2** determined to 74-75°C. R_f in hexane:EtOAc (9:1): 0.65; ^1H NMR spectra of the product **2** showed a singlet at 6.62 ppm with an integral height of 2 that indicated two aromatic protons. A singlet at 4.46 ppm with an integral height of 2 indicated two protons in α position to a carbon-carbon double bond. Two singlets at 3.87 ppm and 3.84 ppm with integral heights of 6 and 3 indicated nine methyl protons.

The product **2** was used in an attempt to synthesize 1,2,3-trimethoxy-5-(prop-2-ynyl)benzene (**3**), as shown in Equation 3.

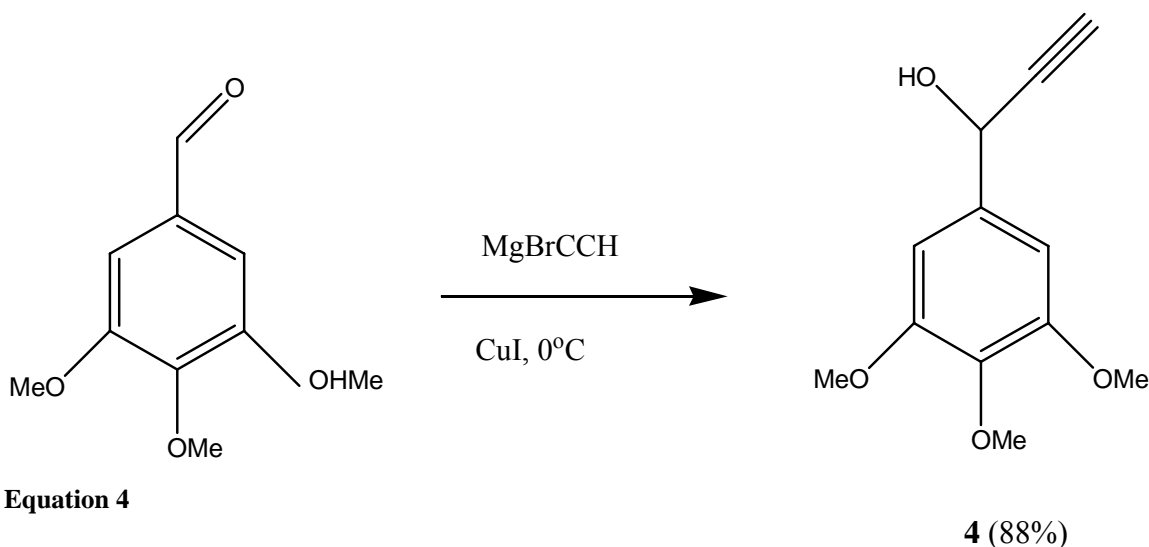


Equation 3

3 (0%)

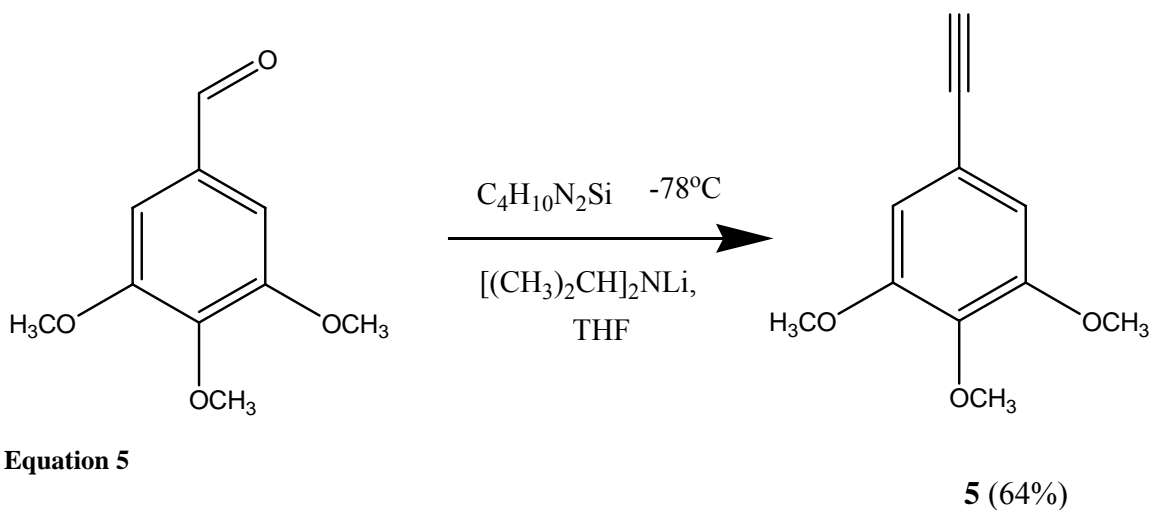
The reaction outlined in Equation 3 was monitored by TLC after 1 hour there was no sign of formation of the product. The temperature was elevated to 58°C and the mixture was left to stir for 48 h. A new test by TLC showed that no product was formed and the experiment was aborted.

A Grignard reaction to obtain a terminal alkyne, as outlined in Equation 4, was performed.



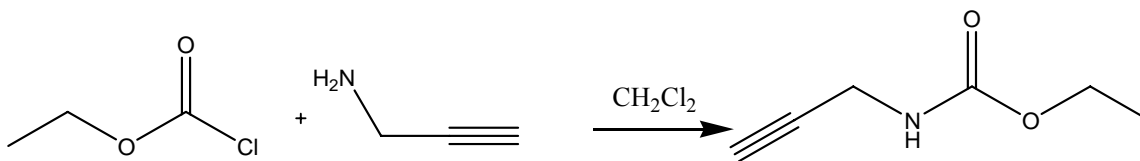
The product 1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (**4**) obtained was not pure. After column chromatography, an 88% yield of **4** was collected. R_f in hexane:EtOAc (1:1): 0.42. ^1H NMR spectra of the product showed a singlet at 6.80 ppm with an integral height of 2 indicated two aromatic protons. A singlet at 5.42 ppm with an integral height of 1 indicated a methine proton. Two singlets at 3.89 ppm and 3.85 ppm with integral heights of 6 and 3 indicated nine methyl protons. A doublet at 2.69 ppm (J 2.1 Hz) indicated an alcohol proton. ^{13}C NMR data showed a peak at 153.87 ppm that indicated two aromatic carbons. Two peaks at 138.10 ppm and 135.56 ppm represented two aromatic carbons. At 103.64 a peak represented two aromatic carbons. Two peaks at 83.56 ppm and 74.89 ppm indicated two acetylene carbons. At 64.56 ppm a peak indicated an aliphatic carbon. At 60.84 ppm and 56.15 ppm two peaks for the three methyl carbons were shown. This confirmed the structure of **4**.

Another terminal alkyne was prepared, this time utilizing dry conditions. The reaction (Equation 5) produced 5-ethynyl-1,2,3-trimethoxybenzene (**5**) in 64% yield after purification by column chromatography.



The melting point of **5** was found to be 93-95°C. R_f in hexane:EtOAc (8:3): 0.50. ^1H NMR spectra of the product showed a singlet at 6.73 ppm with an integral height of 2 that indicated two aromatic protons. A singlet at 3.85 ppm with an integral height of 9 indicated nine methyl protons. A singlet at 3.03 ppm with an integral height of 1 indicated an acetylene proton. ^{13}C NMR data showed a peak at 153.04 ppm that indicated two aromatic carbons. Two peaks at 139.30 ppm and 117.01 ppm represented two aromatic carbons. At 109.36 a peak represented two aromatic carbons. Two peaks at 83.70 ppm and 76.19 ppm indicated two acetylene carbons. At 60.95 ppm and 56.15 ppm two peaks for the three methyl carbons were shown. HRMS data showed that molecular ion was observed at 192.0780 daltons. This confirmed the structure of **5**.

An example of a N-acylation of propargylamine with an acyl chloride to yield ethyl prop-2-ynylcarbamate (**6**) is shown in Equation 6.³⁰

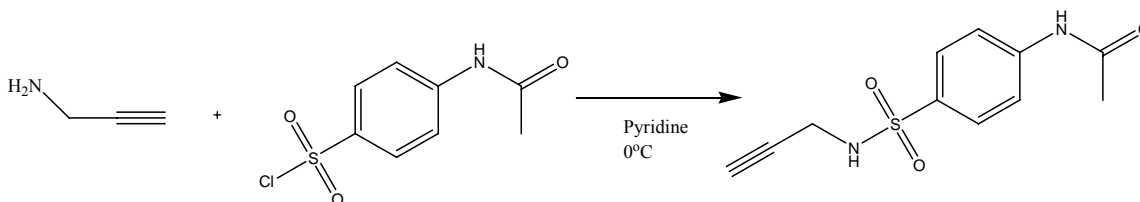


Equation 6

6 (0%)

A NMR of the product (**6**) indicated that only starting materials was isolated.

The N-acylation of propargylamine was performed in the same matter as shown in Equation 6 using a sulfanilylchloride as the other reagent. This reaction is shown in Equation 7.

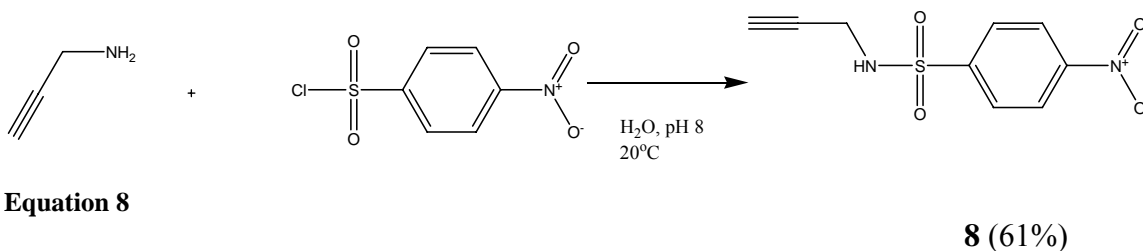


Equation 7

7 (43%)

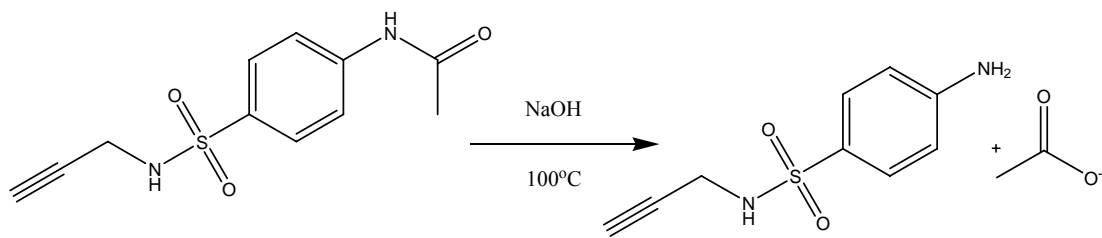
The reaction yielded *N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (**7**). This reaction was performed both on a small scale and a larger scale, using 2 mmol and 45 mmol of propargylamine. The yields were 24% for the small scale reaction and 43% for the larger scale reaction. The structure of the product **7** was assigned based on NMR and MS data as well as the melting point. The melting point was determined to 192-193°C. *R_f* in hexane:EtOAc (1:5): 0.40. ¹H NMR spectra of the product showed a singlet at 9.50 ppm with an integral height of 1 that indicated a sulfonamide proton. A multiplet at 7.84-7.77 ppm with an integral height of 4 indicated four aromatic protons. A multiplet at 3.81-3.79 ppm with an integral height of 2 indicated two methylene protons. A singlet at 2.12 ppm with an integral height of 3 indicated 3 methyl protons. A singlet at 2.09 ppm with an integral height of 1 indicated a secondary amine proton. ¹³C NMR data showed a peak at 170.50 ppm that indicated an amide carbon. Four peaks at 145.15 ppm, 136.45 ppm,

130.08 and 120.37 indicated six aromatic carbons. Two peaks at 80.73 ppm and 74.63 ppm indicated two acetylene carbons. Two peaks at 34.13 ppm and 25.38 ppm indicated two aliphatic carbons. HRMS data showed the molecular ion at 252.0565. This confirmed the structure of **7**.



The structure 4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (**8**) was assigned based on NMR and MS data as well as the melting point. The melting point was determined to $152\text{--}154^\circ\text{C}$. R_f in hexane:EtOAc (2:1): 0.33. ^1H NMR data showed a triplet at 8.54 ppm (J 5.8) with an integral height of 1 that indicated a sulfonamide proton. Two multiplets at 8.45–8.38 ppm and 8.09–8.04 ppm with integral heights of 2 represented four aromatic protons. A doublet of a doublet at 3.79 ppm (J 2.6) with an integral height of 2 represented two aliphatic protons. A triplet at 3.01 ppm (J 2.6) with an integral height of 1 represented an acetylene proton. ^{13}C NMR data showed four peaks at 149.53 ppm, 146.18 ppm, 128.34 ppm, 124.29 ppm that represented six aromatic carbons. Two peaks at 78.72 ppm and 75.09 ppm represented two acetylene carbons. A peak at 31.81 ppm indicated an aliphatic carbon.

An alkaline hydrolysis of **7** to yield 4-amino-*N*-(prop-2-ynyl)benzenesulfonamide (**9**) was performed as outlined in Equation 9.



Equation 9

9 (0%)

TLC of the reaction mixture showed that a product was formed, but there were difficulties with the isolation of the product. It would not be distributed in the organic phase when an extraction with chloroform and water was attempted. The water phase was evaporated under reduced pressure and the resulting solid was dissolved in methanol. The solution was filtered through a “plug”. (Figure 15)

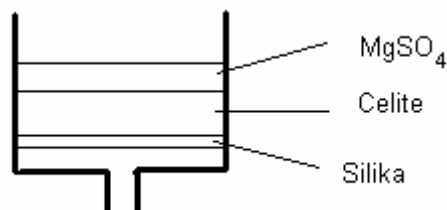


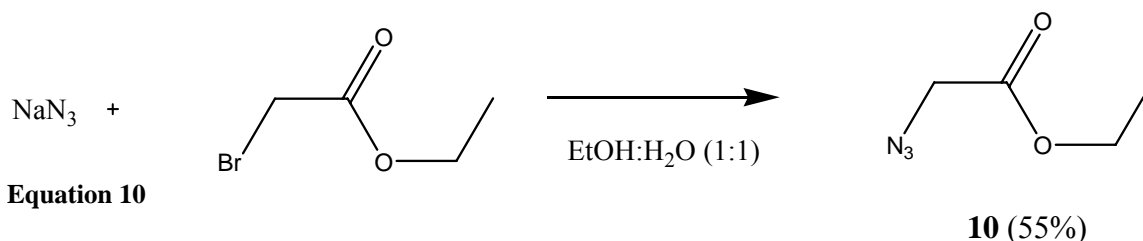
Figure 15: The plug used for filtration of 8

The methanol was evaporated under reduced pressure. The crude product was believed to be a mixture of **9** and sodium chloride, where the sodium chloride originated from the neutralization of the reaction mixture with hydrochloric acid. *R_f* in hexane:EtOAc (1:4) was 0.38. ¹H NMR spectra of the product **9** showed a doublet at 7.53 ppm (*J* 8.7 Hz) with an integral height of 2 that indicated two aromatic protons. A doublet at 6.69 ppm (*J* 9.0 Hz) with an integral height of 2 indicated two aromatic protons. A doublet at 3.65 ppm (*J* 2.7 Hz) with an integral height of 2 indicated two methylene protons. A triplet at 2.47 ppm (*J* 2.7 Hz) with an integral height of 1 indicated a secondary amine proton. A singlet at 2.16 ppm with an integral height of 1 indicated an acetylene proton. ¹³C NMR data showed four peaks at 154.28 ppm, 130.92 ppm, 127.12 and 114.43 that indicated six aromatic carbons. Two peaks at 79.93 ppm and 73.34 ppm indicated two acetylene carbons. At 33.18 ppm a peak indicated an aliphatic carbon. The NMR data showed that

the product was formed, but there were difficulties with the isolation of the product. HRMS data indicated a molecular ion at 210.0457.

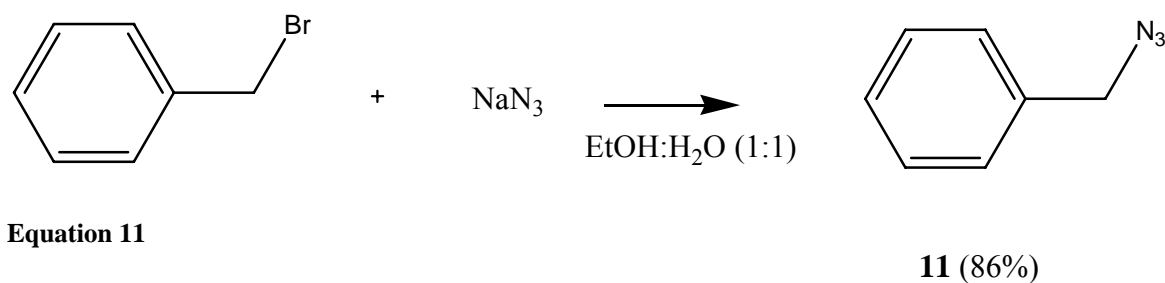
2.1.2 Syntheses of azides.

Several azides were synthesized by nucleophilic substitution (SN2 type). Ethyl 2-azidoacetate (**10**) was synthesized as outlined in Equation 10.



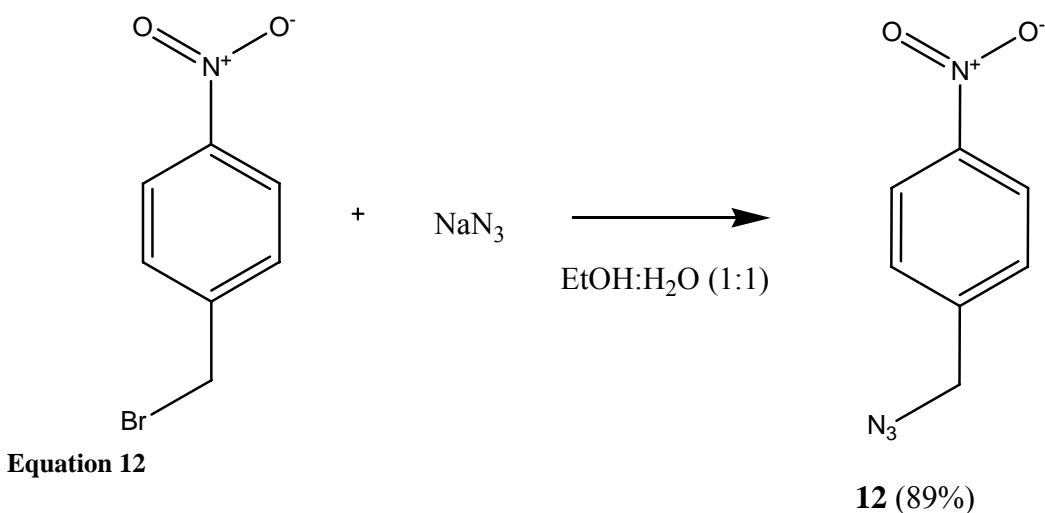
¹H NMR spectra of the product **10** showed a quartet at 4.24 ppm (*J* 6.9 Hz) with an integral height of 2 that indicated two aliphatic protons. A singlet at 3.84 ppm with an integral height of 2 represented the two protons in α-position to the azido group. A doublet 1.29 ppm (*J* 6.9 Hz) with an integral height of 3 indicated three methyl protons. ¹³C NMR data showed a peak at 168.21 ppm that represented a carboxylic carbon. Two peaks at 61.79 ppm and 50.29 ppm represented two aliphatic carbons. A peak at 14.05 represented a methyl carbon. HRMS data indicated the molecular ion at 129.0539. IR data showed signals at 2109 cm⁻¹ for the azido group and 1747 cm⁻¹ for the carbonyl carbon. This confirmed the structure of **10**.

Synthesis of (azidomethyl)benzene (**11**). (Equation 11)



The product **11** had a R_f of 0.80 in hexane:EtOAc (2:1); ^1H NMR spectra showed multiplet at 7.43-7.30 ppm with an integral height of 5 that indicated five aromatic protons. A singlet at 4.35 ppm with an integral height of 2 represented the two protons in α -position to the azido group. ^{13}C NMR data showed four peaks at 135.35, 128.82, 128.29 and 128.20 ppm that represented six aromatic carbons. A peak at 54.80 ppm represented a carbon α -position to the azido group. The product was a yellow liquid.

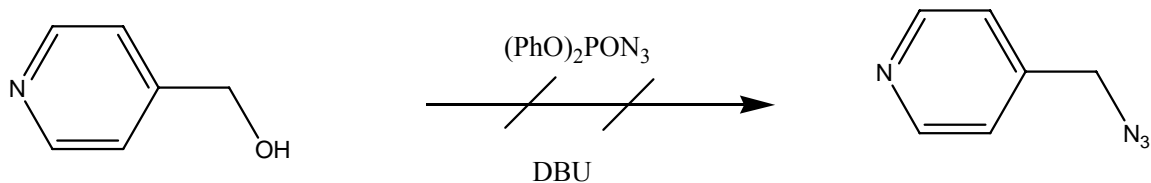
Synthesis of 1-(azidomethyl)-4-nitrobenzene (**12**) (Equation 12).



The product **12** had a R_f of 0.80 in hexane:EtOAc (2:1); ^1H NMR spectra showed multiplet at 8.26-8.19 ppm with an integral height of 2 that indicated 2 aromatic protons. A multiplet at 7.58-7.48 ppm with an integral height of 2 indicated 2 aromatic protons. A singlet at 4.51 ppm with an integral height of 2 represented the two protons in α -position to the azido group. ^{13}C NMR spectrum data showed four peaks at 144.74, 142.67, 129.89 and 124.03 ppm that represented six aromatic carbons. A peak at 53.72 ppm represented a carbon α -position to the azido group. The product was a yellow liquid. HRMS indicated a molecular ion at 178.0490.

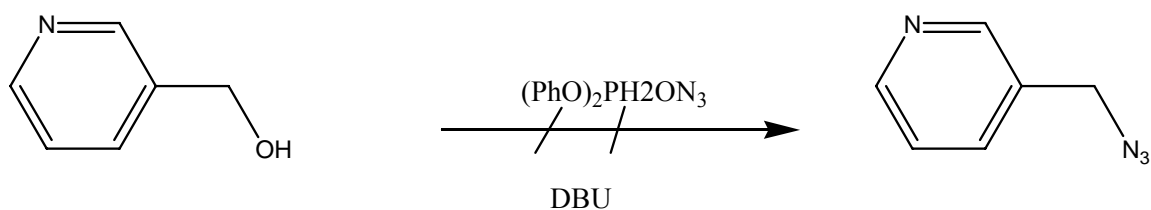
In these experiments it was important to monitor the pH of the mixture before the NaN_3 was added. In acidic aqueous solutions NaN_3 will produce the highly toxic and explosive HN_3 . The experiments were straight forward to perform, and the products were easily isolated via extraction with EtOAc and evaporation under reduced pressure.

Another method for preparation of azides was attempted. A direct conversion of activated alcohols to azides.³¹ (Equation 13 and Equation 14)



Equation 13

13 (0%)



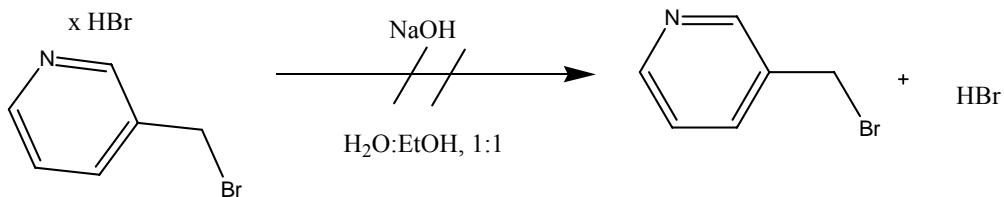
Equation 14

14 (0%)

These two reactions proved difficult to perform and no product was isolated in either one of them.

2.1.3 Desalting of 3-(bromomethyl)pyridine hydrobromide

An attempt to synthesize 3-(bromomethyl)pyridine (**15**) was made. (Equation 15)

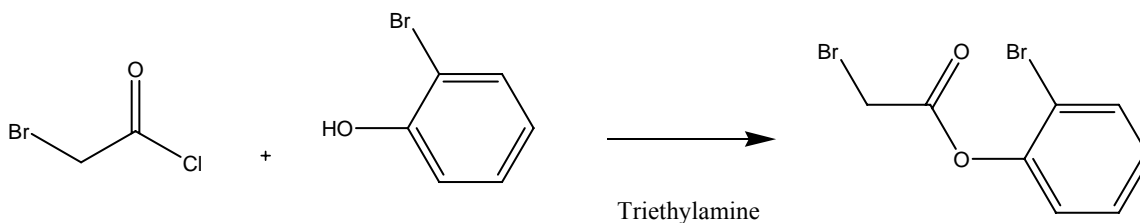


Equation 15

15 (0%)

No product **15** was found when the reaction (Equation 15) was monitored with TLC.

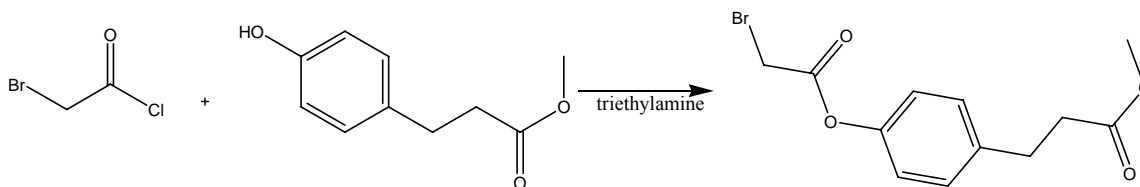
2.1.4 Syntheses of bromides



Equation 16

16 (30%)

The product, 2-bromophenyl 2-bromoacetate (**16**) was obtained as a colorless liquid after column chromatography (Equation 16). The product **16** had a R_f of 0.60 in hexane:EtOAc (3:1). ¹H NMR spectra showed a doublet at 7.62 ppm (J 7.8 Hz) with an integral height of 1, a triplet at 7.35 ppm (J 8.1 Hz) with an integral height of 1 and a multiplet at 7.18-7.13 ppm with an integral height of 2. These three signals represented four aromatic protons. A singlet at 4.37 ppm with an integral height of 2 indicated two aliphatic protons. ¹³C NMR data showed a peak at 164.96 ppm that represented a carboxylic carbon. Six peaks at 147.62 ppm, 133.44 ppm, 128.59 ppm, 127.85 ppm, 123.31 ppm and 115.71 ppm represented six aromatic carbons. At 25.05 ppm a peak indicated an aliphatic carbon.



Equation 17

17 (24%)

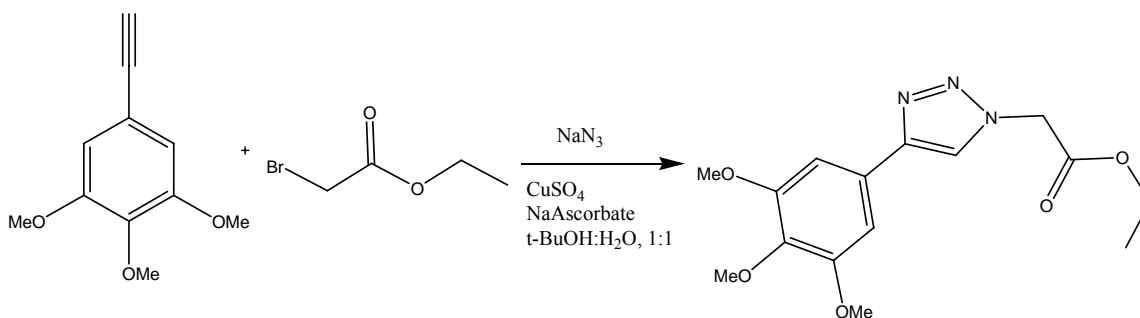
Methyl 3-(4-(2-bromoacetoxy)phenyl)propanoate (**17**) was isolated after column chromatography (Equation 17). The product **17** had a R_f of 0.38 in hexane:EtOAc (3:1); ¹H NMR spectra showed a doublet at 7.23 ppm (J 8.7 Hz) with an integral height of 2 and a doublet at 7.05 ppm (J 8.7 Hz) with an integral height of 2. These two signals represented four aromatic protons. A singlet at 4.27 ppm with an integral height of 2 indicated two aliphatic protons. A singlet at 3.67 ppm with an integral height of 3

indicated three methyl protons. A triplet at 2.96 ppm (J 8.1 Hz) with an integral height of 2 represented 2 aliphatic protons. A triplet at 2.63 ppm (J 7.8 Hz) with an integral height of 2 represented two aliphatic protons. ^{13}C NMR spectrum data showed two peaks at 173.06 ppm and 165.91 that represented two carboxylic carbons. Four peaks at 148.71 ppm, 138.71 ppm, 129.41 ppm and 121.07 ppm represented six aromatic carbons. At 51.65 ppm a peak represented a methyl carbon. At 40.85 ppm, 35.52 ppm and 30.25 ppm three peaks indicated three aliphatic carbons.

2.2 Click reactions

2.2.1 One pot syntheses

Several one pot syntheses was performed to yield 1,4-disubstituted 1,2,3-triazoles. They were performed as described in general procedures for one-pot click reactions. The reactions and results are discussed below.

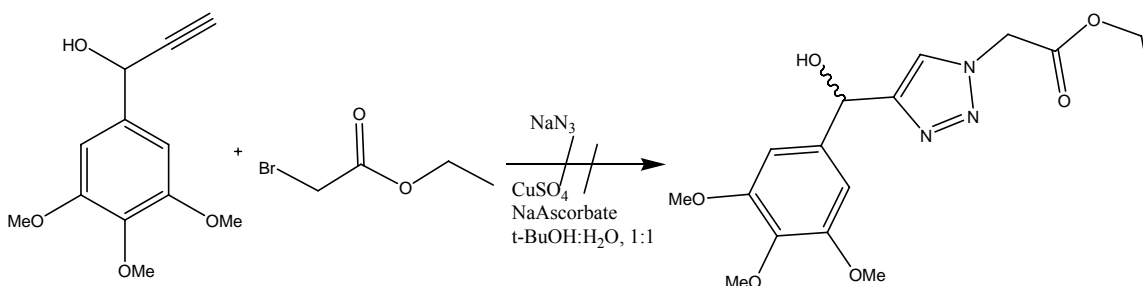


Equation 18

18 (51%)

The synthesis of ethyl 2-(4-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-1-yl)acetate (**18**) did not go to completion after 12 hours of stirring at room temperature. Another 0.5 eqv. of the azide along with more of the sodium ascorbate and the copper sulphate catalyst was added and the mixture was allowed to stir for two more days.. The TLC still indicated traces of the starting materials. Total yield of the reaction was 51%. The melting point was determined to 95-97°C. R_f in hexane:EtOAc (1:10) was 0.66. ^1H NMR spectra of the product **18** showed a singlet at 7.90 ppm with an integral height of 1 that represented the triazole proton. A singlet at 7.06 ppm with an integral height of 2 represented two aromatic protons. A singlet at 5.20 ppm with an integral height of 2 indicated two aliphatic protons. A quartet at 4.29 ppm (J 7.8 Hz) with an integral height of 2 represented two aliphatic protons. Two singlets at 3.92 ppm and 3.87 ppm with integral heights of 6 and 3 indicated nine protons on the methoxy groups. A triplet at 1.31 ppm (J 7.8 Hz) with an integral height of 3 represented three methyl protons. ^{13}C NMR spectrum data showed a peak at 166.27 ppm that represented a carboxylic carbon. Three peaks at 153.62 ppm, 138.24 ppm and 125.84 ppm represented four aromatic carbons. At 120.77 ppm a peak indicated a triazole carbon. At 103.04 a peak indicated two aromatic

carbons. At 62.50 a peak represented an aliphatic carbon. At 60.92 ppm and 56.24 ppm two peaks represented the three carbons in the methoxy groups. At 50.97 ppm and 14.06 ppm two peaks indicated two aliphatic carbons. A peak for the second triazole carbon was not found in the spectrum. HRMS data indicated a molecular ion at 321.1330.

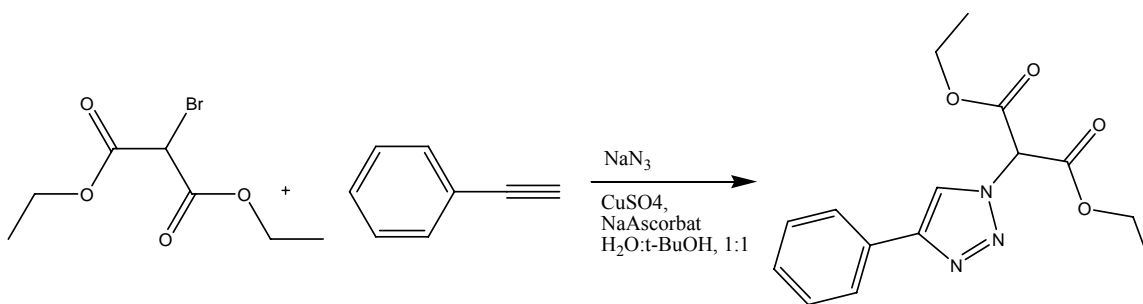


Equation 19

19 (0%)

NMR data of ethyl 2-(4-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**19**) (Equation 19) showed that only starting materials were isolated.

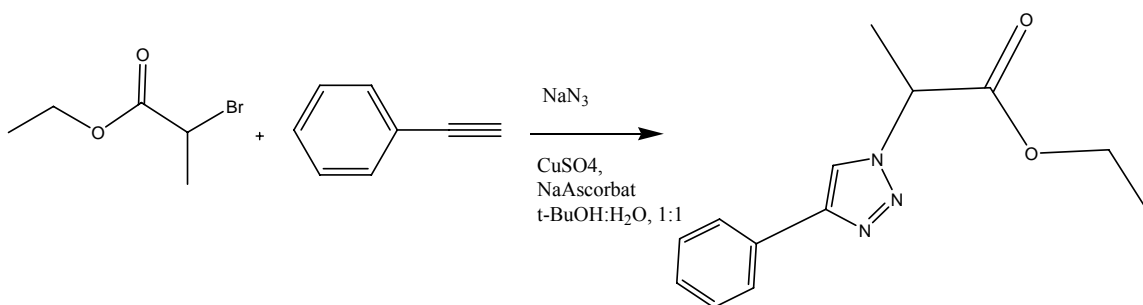
Synthesis of diethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)malonate (**20**) outlined in Equation 20.



Equation 20

20 (25%)

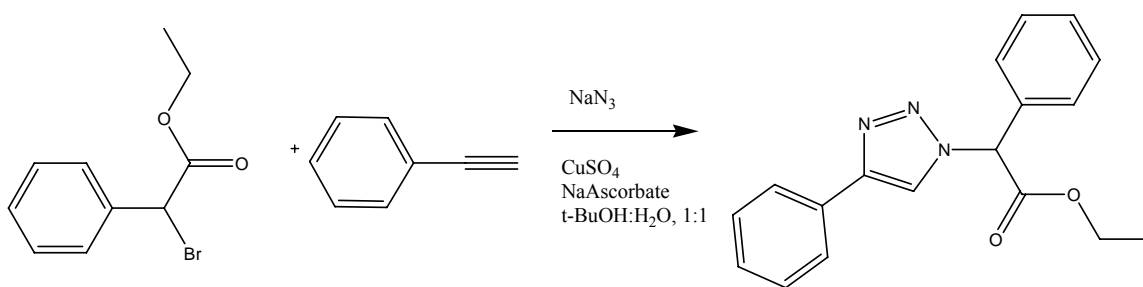
The NMR data showed that the product (**20**) obtained was not pure. (Equation 20)



Equation 21

21 (36%)

The NMR data showed that ethyl 2-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (**21**) obtained was not pure. (Equation 21)



Equation 22

22 (61%)

Synthesis of ethyl 2-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (**22**) (Equation 22). NMR data showed that the product was not formed.



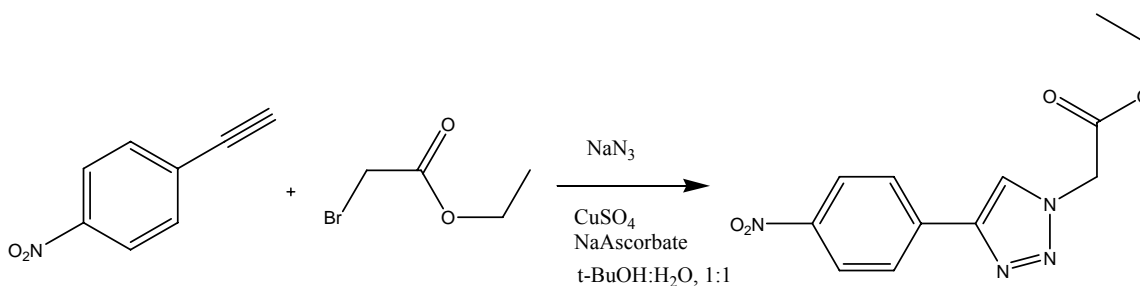
23 (38%)

NMR data of 2-bromophenyl 2-(4-((4-acetamidophenylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**23**) (Equation 23) showed that no product was isolated.



24 (0%)

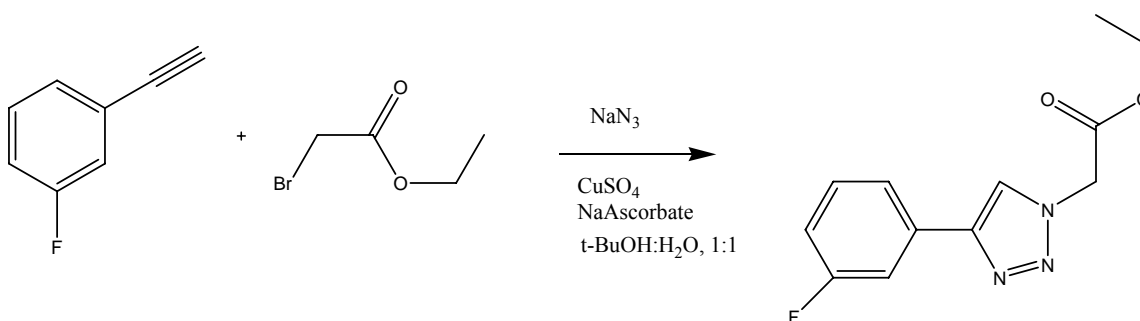
24) TLC monitoring of the reaction showed that no product was formed.



Equation 25

25 (53%)

Synthesis of ethyl 2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)acetate (**25**) (Equation 25). The melting point was determined to 144-145°C. R_f in hexane:EtOAc (1:4) was 0.66. ^1H NMR spectra of the product **25** showed a singlet at 8.85 ppm with an integral height of 1 that represented the triazole proton. A doublet at 8.32 ppm (J 9.0 Hz) with an integral height of 2 represented two aromatic protons. A doublet at 8.14 ppm (J 9.0 Hz) with an integral height of 2 represented two aromatic protons. A singlet at 5.52 ppm with an integral height of 2 indicated two aliphatic protons. A quartet at 4.21 ppm (J 7.2 Hz) with an integral height of 2 represented two aliphatic protons. A triplet at 1.24 ppm (J 7.2 Hz) with an integral height of 3 represented three methyl protons. ^{13}C NMR data showed a peak at 166.98 ppm that represented a carboxylic carbon. At 146.59 ppm a peak indicated a triazole carbon. Two peaks at 144.38 ppm and 136.79 ppm represented two aromatic carbons. At 128.33 ppm a peak indicated a triazole carbon. At 125.94 ppm and 124.23 ppm two peaks indicated four aromatic carbons. At 61.58 ppm and 50.63 ppm two peaks indicated two aliphatic carbons. At 13.89 ppm a peak indicated a methyl carbon. The reaction gave a mixture of the product and the starting materials. The starting materials showed up in the NMR spectrums. Hence, the yield was lower than expected for standard click reactions.

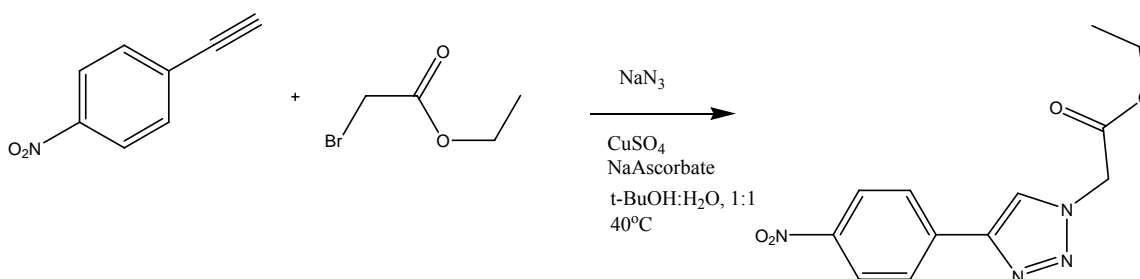


Equation 26

26 (42%)

Synthesis of ethyl 2-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)acetate (**26**). (Equation 26)

The reaction was straight forward, but the yield was lower than expected for standard click reactions. The melting point was found to be over 250°C . R_f in hexane:EtOAc (1:4) was 0.72; ^1H NMR spectra of the product **26** showed a singlet at 8.68 ppm with an integral height of 1 that represented the triazole proton. A multiplet at 7.72-7.14 ppm with an integral height of 4 represented four aromatic protons. A singlet at 5.47 ppm with an integral height of 2 indicated two aliphatic protons. A quartet at 4.20 ppm (J 7.2 Hz) with an integral height of 2 represented two aliphatic protons. A triplet at 1.04 ppm (J 7.2 Hz) with an integral height of 3 represented three methyl protons. HRMS data indicated the molecular ion at 249.0913.

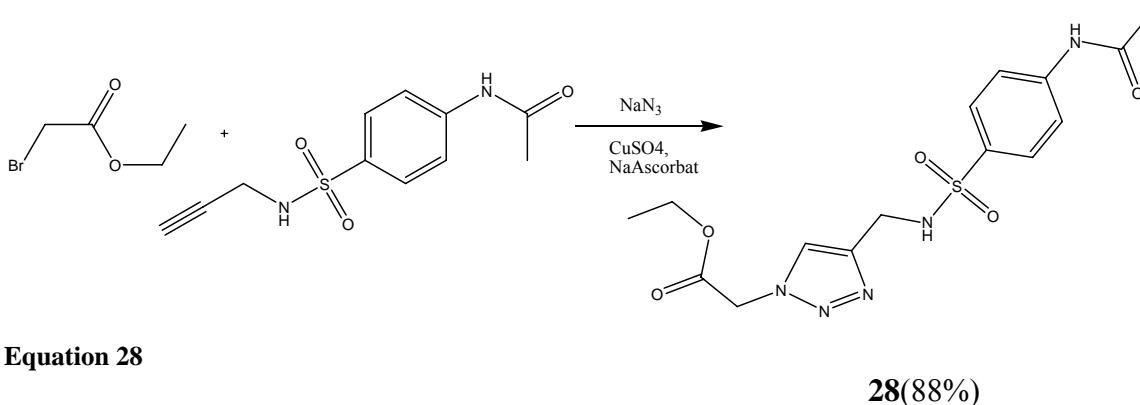


Equation 27

27 (87%)

Synthesis of ethyl 2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)acetate (**27**) (Equation 27).

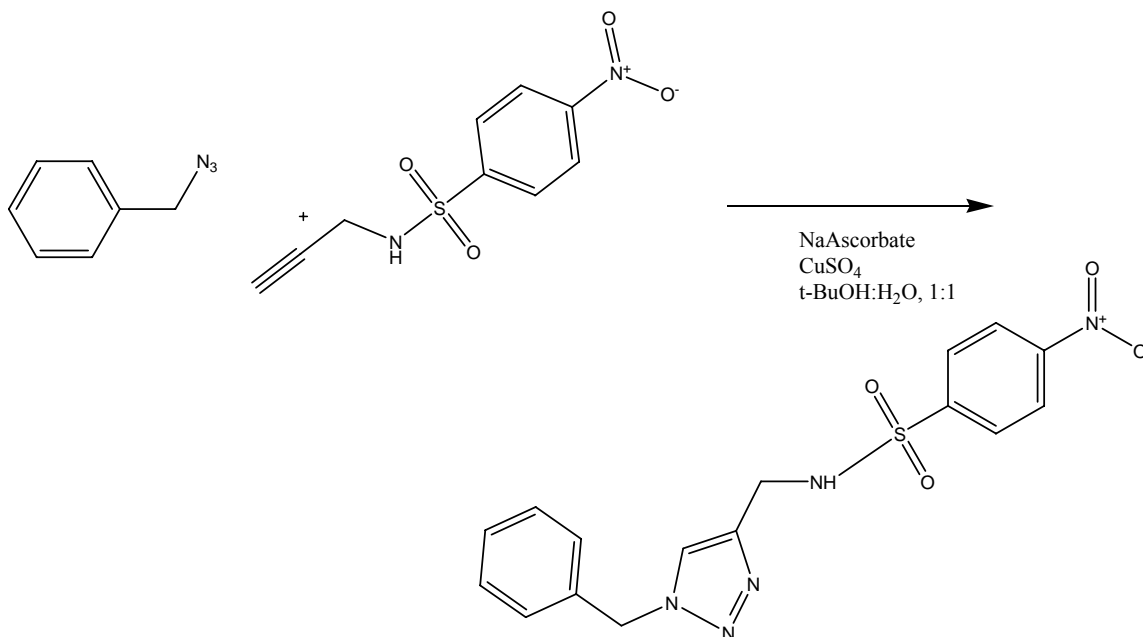
This reaction was a repetition of the one shown in Equation 25 with an elevated temperature. The temperature was now set to 40°C to see if it would result in a better yield. The yield was improved from 53% to 87%, which is in the range for a click reaction. The melting point was determined to 144-145°C. R_f in hexane:EtOAc (1:4) was 0.66. ^1H NMR spectra of the product (**27**) showed a singlet at 8.84 ppm with an integral height of 1 that represented the triazole proton. Two doublets at 8.33 ppm (J 9.0 Hz) and 8.14 ppm (J 9.0 Hz), both with an integral height of 2 represented four aromatic protons. A singlet at 5.14 ppm with an integral height of 2 indicated two aliphatic protons. A quartet at 4.21 ppm (J 7.2 Hz) with an integral height of 2 represented two aliphatic protons. A triplet at 1.24 ppm (J 7.2 Hz) with an integral height of 3 represented three methyl protons. These results were in concordance with the results for **25**.



Synthesis of ethyl 2-((4-((4-acetamidophenyl)sulfonamido)methyl)-1*H*-pyrazol-1-yl)acetate (**28**) (Equation 28). The product was isolated as white crystals. The melting point was determined to 176-178°C. ^1H NMR spectra of the product **28** showed a singlet at 10.31 ppm with an integral height of 1 that represented a secondary amide proton. A singlet at 8.03 ppm with an integral height of 1 indicated a sulfonamide proton. A singlet at 7.92 ppm with an integral height of 1 indicated a triazole proton. A multiplet at 7.80-7.65 ppm with an integral height of 4 indicated four aromatic protons. A singlet at 5.32 ppm with an integral height of 2 represented two aliphatic protons. A quartet at 4.17 ppm (J 7.1 Hz) with an integral height of 2 represented two protons in α -position to the ester. A singlet at 4.03 with an integral height of 2 represented two aliphatic protons. A singlet at 2.09 with an integral height of 3 represented three methyl protons. A triplet at 1.22 (J

7.1 Hz) with an integral height of 3 represented three methyl protons. ^{13}C NMR data showed two peaks at 168.87 and 167.07 that indicated two carbonyl carbons. Four peaks at 142.67, 133.82, 127.64 and 124.61 represented 6 aromatic carbons. A peak at 118.48 represented a triazole carbon. Five peaks at 61.35, 50.17, 38.60, 24.04 and 13.88 represented five aliphatic carbons. There was not found a peak for the second triazole carbon. HRMS calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_5\text{O}_5\text{S}$ [M^+]: 381.1107, found: 381.1074

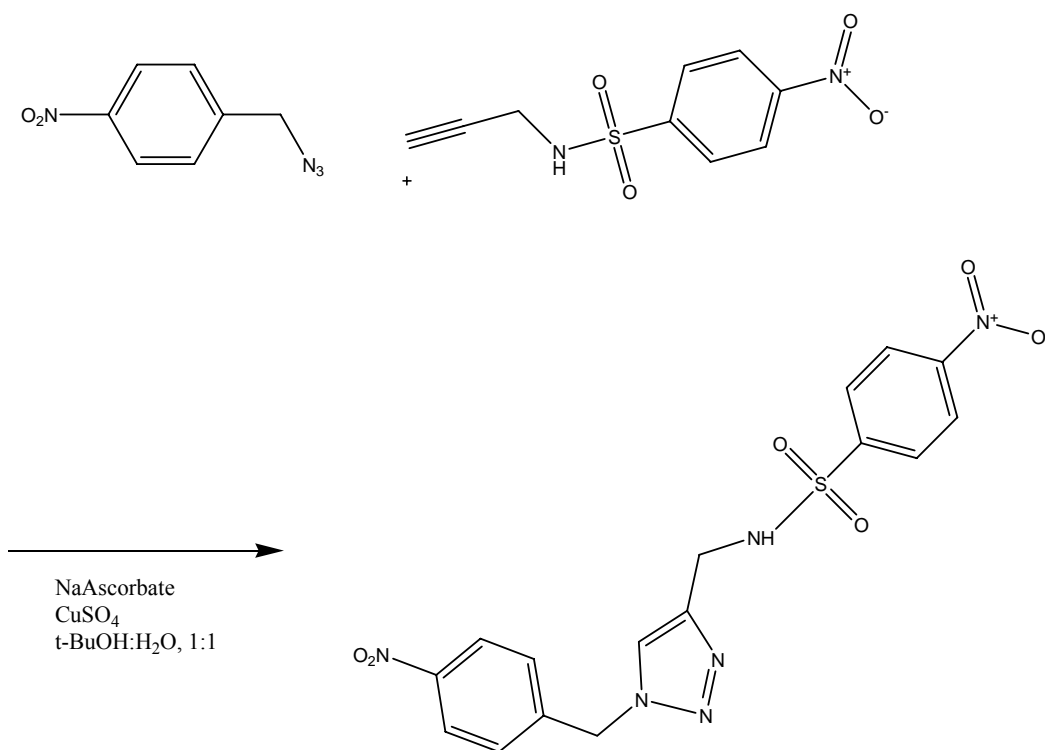
2.2.2 1,4 Disubstituted cyclo additions



Equation 29

29 (74%)

Synthesis of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-nitrobenzenesulfonamide (**29**). The melting point was determined to 144-145°C. R_f in hexane:EtOAc (1:4) was 0.56. ^1H NMR spectra of the product **29** showed a singlet at 8.53 ppm with an integral height of 1 that represented the sulfonamide proton. A doublet at 8.31 ppm (J 9.0 Hz) with an integral height of 2 represented 2 benzene protons. A doublet at 7.97 ppm (J 9.0 Hz) with an integral height of 2 represented two benzene protons. At 7.90 ppm a singlet with an integral height of 1 represented a triazole proton. A multiplet at 7.35-7.22 ppm with an integral height of 5 represented five aromatic protons. A singlet at 5.49 ppm with an integral height of 2 indicated two aliphatic protons. A singlet at 4.14 ppm with an integral height of 2 indicated two aliphatic protons. ^{13}C NMR data showed four peaks at 149.32 ppm, 146.10 ppm, 135.80 ppm and 128.58 ppm that represented five aromatic carbons. At 128.06 ppm a peak indicated a triazole carbon. Four peaks at 127.99 ppm, 127.83 ppm, 124.29 and 123.34 ppm indicated seven aromatic carbons. At 52.59 ppm and 37.83 ppm two peaks indicated two aliphatic carbons. One of the peaks for the carbons on the triazole did not show up in the spectrum.

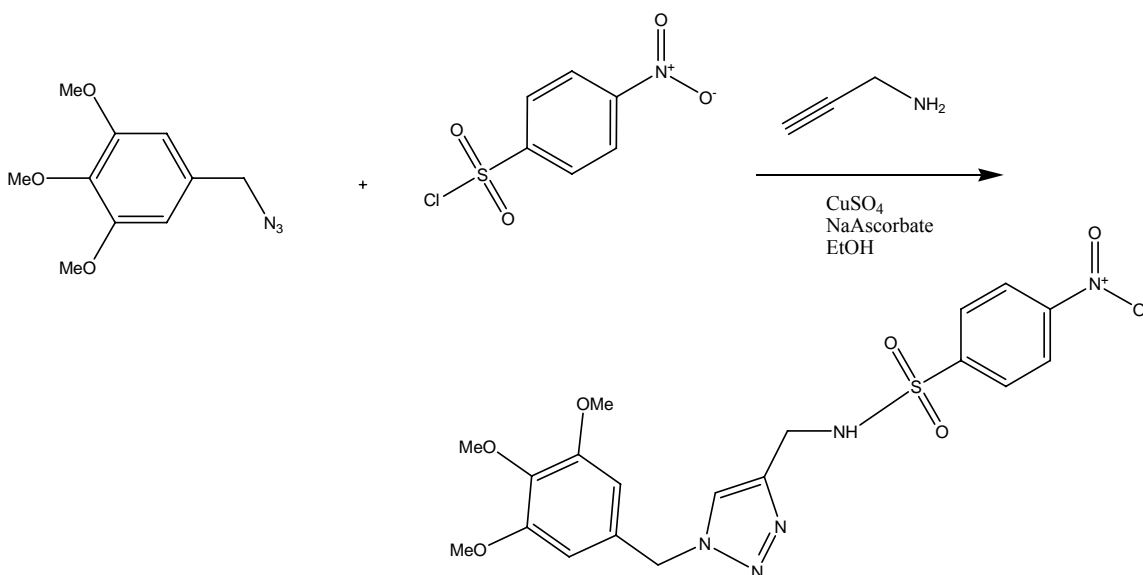


Equation 30

30 (52%)

The reaction outlined in Equation 30 was performed twice. The first time over, the product obtained was impure. This was probably due to insufficient use of solvent. Only 4 mL was used. 8 mL of solvent was used in the second experiment. The reaction gave 4-nitro-*N*-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**30**) in a 52% yield. The melting point was determined to 183-185°C. *R_f* in hexane:EtOAc (1:4) was 0.36. ¹H NMR spectra of the product **30** showed a singlet at 8.58 ppm with an integral height of 1 that represented the sulfonamide proton. A doublet at 8.31 ppm (*J* 8.7 Hz) with an integral height of 2 represented two benzene protons. A doublet at 8.22 ppm (*J* 8.7 Hz) with an integral height of 2 represented two aromatic protons. At 7.99 ppm (*J* 8.4 Hz) a doublet with an integral height of 3 represented two aromatic protons and an overlapping triazole proton. A doublet at 7.47 ppm (*J* 8.7 Hz) with an integral height of 2 represented two aromatic protons. A singlet at 5.69 ppm with an integral height of 2 indicated two aliphatic protons. A singlet at 4.17 ppm with an integral height of 2 indicated two aliphatic protons. ¹³C NMR data showed four peaks at 149.26 ppm, 147.11

ppm, 146.08 ppm and 143.15 ppm that represented four aromatic carbons. Four peaks at 128.88 ppm, 127.97 ppm, 124.26 ppm and 123.70 ppm represented eight aromatic carbons. At 58.91 ppm and 37.82 ppm two peaks represented two aliphatic carbons.

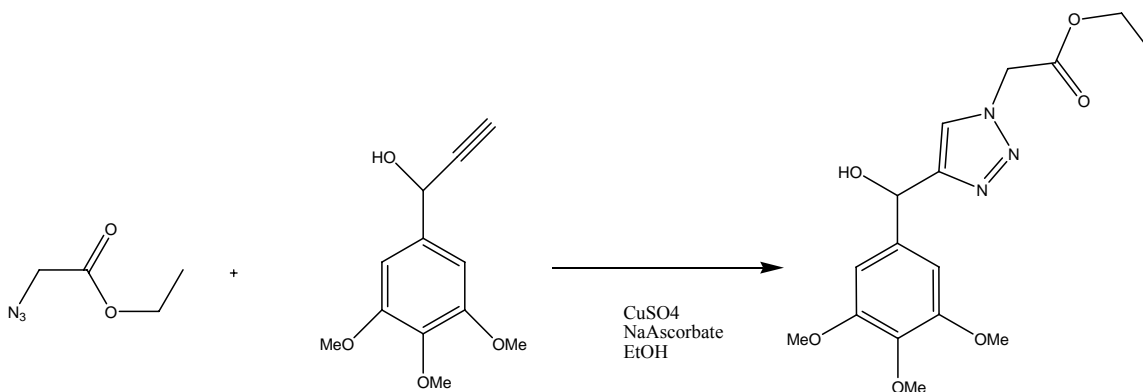


Equation 31

31 (42%)

Synthesis of 4-nitro-*N*-((1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**31**) (Equation 31). The melting point was determined to 148-154°C. R_f in hexane:EtOAc (1:4) was 0.32. ^1H NMR spectra of the product **31** showed a singlet at 8.51 ppm with an integral height of 1 that represented the sulfonamide proton. A doublet at 8.34 ppm (J 9.0 Hz) with an integral height of 2 represented two aromatic protons. A doublet at 8.00 ppm (J 9.0 Hz) with an integral height of 3 represented two aromatic protons and an overlapping triazole proton. A singlet at 6.67 ppm with an integral height of 2 represented two aromatic protons. A singlet at 5.41 ppm with an integral height of 2 indicated two aliphatic protons in α -position to benzene. A singlet at 4.12 ppm with an integral height of 2 indicated two aliphatic protons in α -position to the triazole. Two singlets at 3.75 ppm and 3.63 ppm with integral heights of 6 and 3 indicated nine methoxy protons. ^{13}C NMR data showed three peaks at 152.90 ppm, 149.39 ppm and 145.95 ppm that represented four aromatic carbons. At 143.20 ppm a peak indicated a triazole carbon. Four peaks at 137.26 ppm,

131.18 ppm, 128.04 ppm and 124.31 pm indicated six aromatic carbons. At 123.30 ppm a peak indicated a triazole carbon. At 59.88 ppm and 55.84 ppm two peaks represented the three carbons in the methoxy groups. At 52.81 ppm and 37.20 ppm two peaks indicated two aliphatic carbons.



Equation 32

32 (58%)

Synthesis of ethyl 2-(4-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (**32**) (Equation 32). NMR results indicated that a mixture of **32** and **32** without the hydroxyl group were formed. The product was not purified by column chromatography.

3. Experimental

3.1 General procedures

General procedure for click reactions

The click reactions were performed as outlined below. The individual data are given in the description of the different syntheses. An azide was mixed with t-BuOH:H₂O (1:1) in a 20 mL screw-top scintillation vial. An alkyne and sodium ascorbate was added. The mixture was stirred at room temperature until everything were dissolved. Finally copper sulphate was added, and the mixture was allowed to stir at room temperature over night. The reaction mixture was diluted with ice-water and a precipitate usually formed. The precipitate was filtered off and washed 3 times with saturated ammonium chloride solution and 2 times with cold diethyl ether. This was the standard procedure for isolation of the product, unless another method is described for the individual experiments.

General procedure for one-pot click reactions

The one-pot click reactions were performed as outlined below. The individual data are given in the description of the different syntheses. A bromide was mixed with t-BuOH:H₂O (1:1) in a 20 mL screw-top scintillation vial. Sodium azide, an alkyne and sodium ascorbate was added. The mixture was stirred at room temperature until everything were dissolved. Finally copper sulphate was added, and the mixture was allowed to stir at room temperature over night. The reaction mixture was diluted with ice-water and a precipitate usually formed. The precipitate was filtered off and washed 3 times with saturated ammonium chloride solution and 2 times with cold diethyl ether. This was the standard procedure for isolation of the product, unless another method is described for the individual experiments.

General procedure to prepare azides

The amounts of the different compounds and data for the individual reactions are given below. The experiments were carried out at room temperature. Solvent (EtOH:H₂O, 1:1) was put in a round bottomed flask of a proper size, and the pH was measured. If the pH

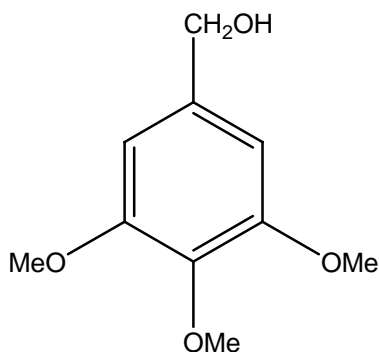
was not around 7, some HCO_3^- (aq) or HCl was added. NaN_3 was added to the solvent while stirring. The bromide was added to the mixture while stirring. The mixture stirred for 12 hours. EtOAc in equal volumes to the solvent was added to the mixture. The mixture was washed with brine in equal volumes twice. The organic phase was dried (MgSO_4) and the organic solvent was evaporated under reduced pressure.

General procedure to prepare bromides

The amounts of the different compounds and data for the individual reactions are given separately in the description for each experiment. The experiments were carried out at under dry conditions at room temperature. The alcohol was weighed in a round bottomed flask of suitable size and it was flushed with Argon. Dichloromethane was added to the round bottomed flask via a syringe. Triethylamine was added via a syringe while stirring. Bromoacetylchloride was added drop by drop via a syringe. The mixture was allowed to stir over night. NaHCO_3 (10%) was added until the bobbling stopped. The mixture was washed with brine. The organic phase was dried (MgSO_4) and the solvent was evaporated under reduced pressure. Column chromatography was performed on the products.

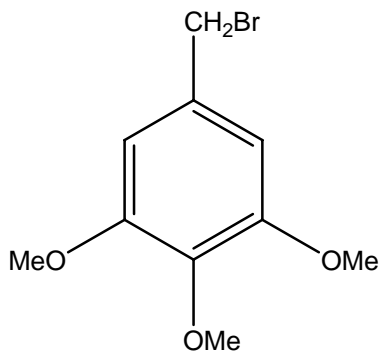
3.2 Synthesis

(3,4,5-Trimethoxy)methanol (1)



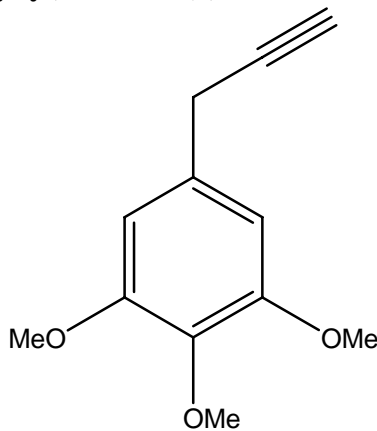
NaBH₄ (0.76g, 20 mmol) was dissolved in EtOH:H₂O (1:1, 20 mL) while stirring at 0°C. 3,4,5-Trimethoxybenzaldehyde (7.85 g, 40mmol) was dissolved in THF:EtOH (1:3, 60 ml). The NaBH₄ solution was added, in small portions, to the 3,4,5-trimethoxybenzaldehyde solution at 0°C while stirring. After 5 min. the ice bath was removed, and the mixture was stirred at room temperature for 2.5 hours. The reaction was quenched with ice. The mixture was acidified to pH 1 with HCl (conc.), extracted with EtOAc (3x100 mL), washed with brine (2x100 mL) and dried (MgSO₄). The MgSO₄ was filtered off and the solvent was evaporated under reduced pressure furnishing 8.03 g (total yield 100%) as a slightly yellow colored oil. ¹H NMR (CDCl₃, 300 MHz) δ 6.58 (s, 2H), 4.62 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 2.03 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.30, 137.23, 136.63, 103.75, 65.43, 60.80, 56.03.

5-(bromomethyl)-1,2,3-trimethoxybenzene (2)



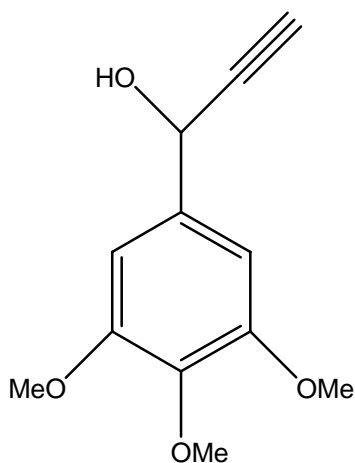
The experiment was performed under dry conditions. (3,4,5-Trimethoxy)methanol (0.99g, 5 mmol) was dissolved in dichloromethane (10 mL) while stirring. CBr_4 (1.70g, 6 mmol) was added and dissolved. The mixture was put on an ice bath and the flask was flushed with argon. Triphenylphosphine (1.71g, 6.5 mmol) was added in small portions. The mixture was taken off the ice bath and was left to stir for over night at room temperature. The mixture was washed with hexane (2x 20 mL) and CHCl_3 (2x20 mL), this caused precipitation. The mixture was filtered through silica 2x. The solvent was evaporated under reduced pressure, furnishing 3.92g (total yield 58%) as white crystals. Mp: 74-75°C; ^1H NMR (CDCl_3 , 300 MHz) δ 6.58 (s, 2H), δ 4.62 (s, 2H), δ 3.85 (s, 6H), δ 3.82 (s, 3H), δ 2.03 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 153.30, 137.23, 136.63, 103.75, 65.43, 60.80, 56.03.

1,2,3-trimethoxy-5-(prop-2-ynyl)benzene (3)



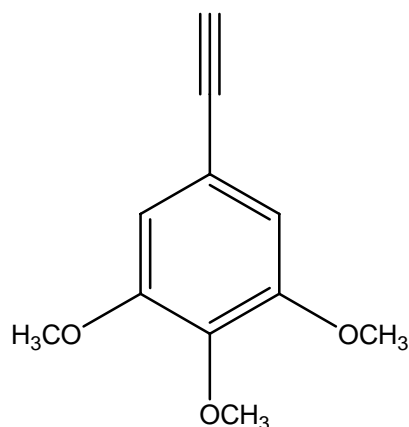
The experiment was performed under dry conditions. 5-(bromomethyl)-1,2-dimethoxy-3-methylbenzene (0.66g, 2 mmol) and CuI (0.04g, 0.2 mmol) was weighed out in a flask. The flask was flushed with N_2 . Dry THF (10 mL) was added and the mixture was stirred until the solids dissolved. Ethynylmagnesium bromide in THF (0.5M, 8 mL) was added. The mixture was stirred for 48 hours at 58°C. TLC showed that no product was formed. The experiment was aborted.

1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (4)



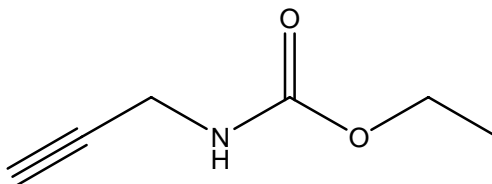
The experiment was performed under dry conditions. 3,4,5-trimethoxybenzaldehyde (1.96g, 10 mmol) and was weighed out in a flask. The flask was flushed with Argon. Dry THF (20 mL) was added and the mixture was stirred until the solid dissolved. The mixture was put on an ice bath. Ethynylmagnesium bromide in THF (0.5M, 24 mL) was added. The mixture was stirred for 1 hour at 0°C. After 1 hour the ice bath was removed and the mixture was stirred over night. TLC showed that product was formed. NH₄Cl (20 mL) was added. The organic phase and the water phase were separated. The water phase was extracted twice with diethyl ether and washed with brine. The organic phase was collected and dried (MgSO₄) and the solvent was evaporated under reduced pressure. Flashchromatography was performed, furnishing 1.96g (total yield 88%) as white crystals; R_f 0.42 (hexane:EtOAc, 1:1); ¹H NMR (CDCl₃, 300 MHz) δ 6.80 (s, 2H), 4.62 (s, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 2.69 (d, *J* 2.1 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.87, 138.10, 135.56, 103.64, 83.56, 74.89, 64.56, 60.84, 56.15.

5-ethynyl-1,2,3-trimethoxybenzene (5)



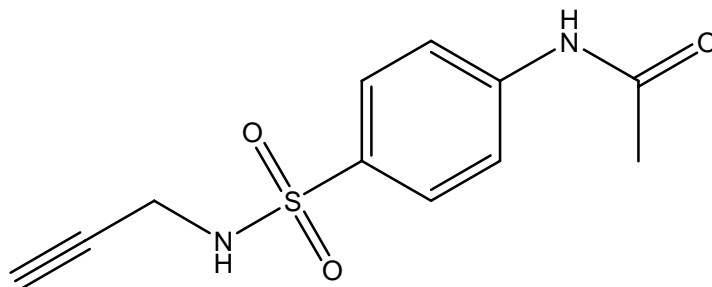
The experiment was performed under dry conditions. A bath of acetone and dry ice was prepared. A 250 mL round bottomed flask was flushed with Argon and put in the acetone/dry ice bath. $[(\text{CH}_3)_2\text{CH}]_2\text{NLi}$ (1.8 M, 23.3 mL) measured out and transferred to the round bottomed flask. $\text{C}_4\text{H}_{10}\text{N}_2\text{Si}$ (2.0 M, 18.8 mL) was carefully added. After 15 minutes, 3,4,5-trimethoxybenzaldehyde (5.89 g, 30 mmol) was weighed out and dissolved in dry THF and added drop by drop to the mixture. The mixture was allowed to stir over night at -78°C . The mixture was brought to room temperature. Brine (30 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine (2 x 100 mL). The organic phase was collected and dried (MgSO_4) and the solvent was evaporated under reduced pressure. Column chromatography was performed, furnishing 3.69 g (total yield 64%) as white crystals; mp $93\text{--}95^\circ\text{C}$; R_f 0.50 (Hexane:EtOAc 8:3); ^1H NMR (CDCl_3 , 300 MHz) δ 6.73 (s, 2H), 3.85 (s, 9H), 3.03 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 153.04, 139.30, 117.01, 109.36, 83.70, 76.19, 60.95, 56.15; HRMS calcd. for Chemical Formula: $\text{C}_{11}\text{H}_{12}\text{O}_3$ [M^+]: 192.0786, found: 192.0780.

Ethyl prop-2-ynylcarbamate (6)



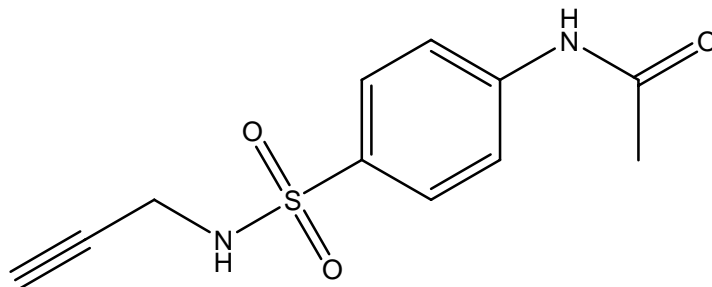
An ice bath was prepared. Propargylamine (0.54 g, 5 mmol) was dissolved in dichloromethane (5 mL). Ethylchloroformate (0.27 g, 5 mmol) was dissolved in dichloromethane (5 mL). The Propargylamine solution was added to the Ethylchloroformate solution drop by drop while stirring at 0°C. The mixture was stirred over night at room temperature. EtOAc (50 mL) was added. The mixture was washed with NaHCO₃ (20%, 2 x 50 mL). The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced. NMR data indicated that only starting materials were isolated.

***N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (7)**



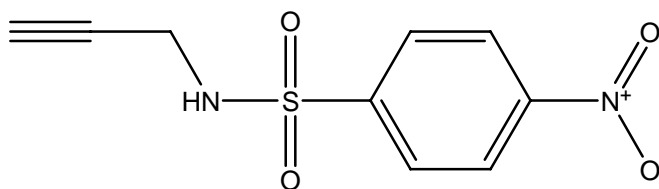
An ice bath prepared. Propargylamine (0.20 g, 2 mmol) was weighed in 25 mL round bottomed flask. Pyridine (1 mL) was added, and the solution was stirred at 0°C. *N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (0.43 g, 1.85 mmol) was added in small portions. The mixture was stirred over night at room temperature. HCl (1M, 10 mL) and EtOAc (20 mL) was added. The organic phase was washed with HCl (1 M, 10 x 10 mL). The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced pressure, furnishing 0.11 g (total yield 24%) as pink crystals; mp 192-193°C; R_f 0.40 (Hexane:EtOAc 1:5); ¹H NMR (d-Aceton, 300MHz) δ= 9.49 (s, 1H), 7.84-7.77 (m, 4H), 3.81-3.79 (m, 2H), 2.12 (s, 3H), 2.09 (s, 1H); ¹³C NMR (d-Aceton, 75 MHz) δ 170.50, 145.15, 136.45, 130.08, 120.37, 80.73, 74.63, 34.13, 25.38; HRMS calcd. for C₁₁H₁₂N₂O₃S [M⁺]: 252.0569 found: 252.0565.

***N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (7)**



Large scale preparation of (7): an ice bath prepared. Propargylamine (2.48 g, 45 mmol) was weighed in 250 mL round bottomed flask. Pyridine (40 mL) was added, and the solution was stirred at 0°C. The round bottomed flask was flushed with Argon. *N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (6.71g, 30 mmol) was added in small portions. The mixture was stirred over night at room temperature. HCl (2 M, 70 mL) and EtOAc (100 mL) was added. The organic phase was washed with HCl (2 M, 10 x 70 mL). The resulting precipitate was filtered off, furnishing 3.25 g (total yield 43%) as pink crystals; mp 192-193°C; R_f 0.40 (Hexane:EtOAc 1:5); ^1H NMR (CDCl_3 , 300 MHz) δ 9.50 (s, 1H), 7.84-7.77 (m, 4H), 3.81-3.79 (m, 2H), 2.12 (s, 3H), 2.01 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.50, 145.15, 136.45, 130.08, 120.37, 80.73, 74.63, 34.13, 25.38; HRMS calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ [M^+]: 252.0569 found: 252.0565.

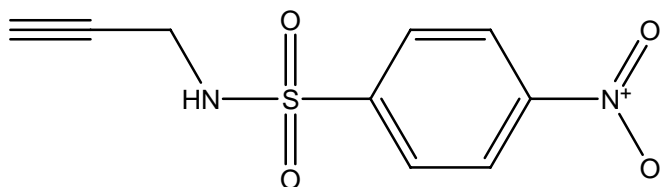
4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (8)



An ice bath prepared. Propargylamine (1.69 g, 30 mmol) was weighed in 250 mL round bottomed flask. Pyridine (30 mL) was added, and the solution was stirred at 0°C. The round bottomed flask was flushed with Argon. 4-nitrobenzene-1-sulfonyl chloride (4.93 g, 20 mmol) was added in small portions. The mixture was stirred over night at room temperature. HCl (2 M, 70 mL) and EtOAc (100 mL) was added. The organic phase was washed with HCl (2 M, 10 x 70 mL). The mixture was brought to pH 7 with NaOH

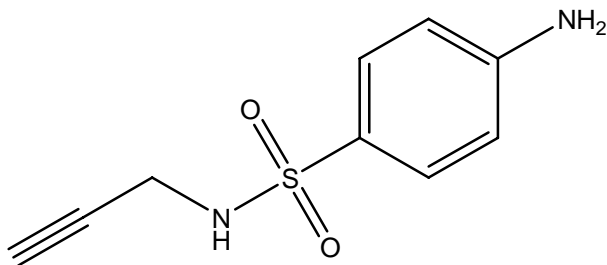
(6M). The resulting precipitate was filtered off, furnishing 3.12 g (total yield 61%) as a yellow solid; mp 152-154°C; R_f 0.33 (Hexane:EtOAc, 2:1); ^1H NMR (DMSO, 200 MHz) δ 8.54 (t, J 5.8 Hz, 1H), 8.45-8.38 (m, 2H), 8.09-8.04 (m, 2H), 3.79 (dd, J 2.6, 2H), 3.01 (t, J 2.6 Hz, 1H); ^{13}C NMR (DMSO, 75 MHz) δ 149.53, 146.18, 128.34, 124.29, 78.72, 75.09, 31, 81.

4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (8)



Propargylamine (0.23 g, 4 mmol) was weighed in 100 mL round bottomed flask. 4-nitrobenzene-1-sulfonyl chloride (0.99 g, 4 mmol) and water (20 mL) was added. The pH of the mixture was adjusted to 8 with Na_2CO_3 . The mixture was stirred at room temperature and Na_2CO_3 was added to keep the pH at 8. After 2 hours the reaction was stopped by adding HCl (12 M, 1 mL). The resulting precipitate was filtered off and washed with water.

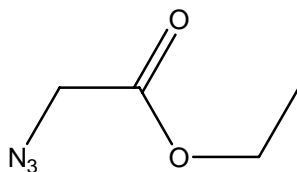
4-amino-*N*-(prop-2-ynyl)benzenesulfonamide (9)



N-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (1.51 g, 6 mmol) and NaOH (10 M, 60 mL) was refluxed 3 hours in a 250 mL round bottomed flask with a cooler. The mixture was neutralized with HCl (3 M). NaOH (0.01 M) was added to make the mixture slightly

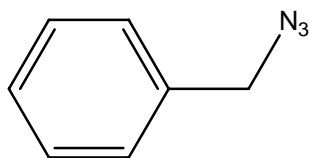
alkaline. The mixture was extracted with chloroform (3 x 100 mL), but the product did not distribute in the organic phase. The water phase was evaporated under reduced pressure and the resulting solid was dissolved in methanol. The solution was filtered through a “plug” of MgSO₄, celite and silica. *R_f* 0.38 (Hexane:EtOAc 1:4); ¹H NMR (d₆-MeOH, 300 MHz); δ 7.53 (d, *J* 8.7 Hz, 2H), 6.69 (d, *J* 9.0 Hz, 2H), 3.65 (d, *J* 2.7 Hz, 2H), 2.47 (t, *J* 2.7 Hz, 1H), 2.16 (s, 1H); ¹³C NMR (d₆-MeOH, 75 MHz) δ 154.28, 130.92, 127.12, 114.43, 79.93, 73.34, 33.18; HRMS calcd. for C₉H₁₀N₂O₂S [M⁺]: 210.0463, found: 210.0457.

Ethyl 2-azidoacetate (10)



Ethyl 2-azidoacetate was prepared according to the general procedure for azides from ethyl 2-bromoacetate (0.84 g, 5 mmol) and sodium azide (0.34 g, 5.25 mmol), furnishing 0.37 g (55%) as a colorless liquid. IR: 2109 cm⁻¹, 1747 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.24 (q, *J* 6.9 Hz, 2 H), 3.84 (s, 2H), 1.29 (d, *J* 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.21, 61.79, 50.29, 14.05; HRMS calcd. for C₄H₇N₃O₂ [M⁺]: 129.0538, found: 129.0539.

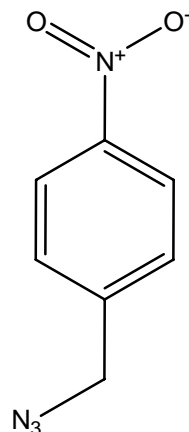
(Azidomethyl)benzene (11)



(Azidomethyl)benzene was prepared according to the general procedure for azides from benzyl bromide (3.42 g, 20 mmol) and sodium azide (1.37 g, 21 mmol), EtOH:H₂O (1;1, 80 mL). The reaction yielded 2.28 g (86%) as a yellow liquid; *R_f* 0.80 (Hexane:EtOAc

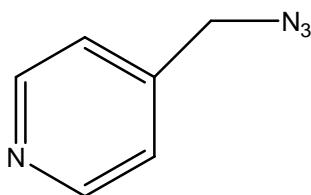
2:1); ^1H NMR (CDCl_3 , 300 MHz) δ 7.43-7.30 (m, 5 H), 4.35 (s, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 135.35, 128.82, 128.29, 128.20, 54.80

1-(Azidomethyl)-4-nitrobenzene (12)



1-(Azidomethyl)-4-nitrobenzene was prepared according to the general procedure for azides from 4-nitrobenzyl bromide (3.42 g, 20 mmol) and sodium azide (1.37 g, 21 mmol). The reaction yielded 3.56 g (89%) as a yellow liquid; R_f 0.74 (Hexane:EtOAc 1:4); ^1H NMR (CDCl_3 , 300 MHz) δ 8.26-8.19 (m, 2 H), 7.58-7.48 (m, 2H), 4.51 (s, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 144.74, 142.67, 129.89, 124.03, 53.72 ; HRMS calc for $\text{C}_6\text{H}_6\text{N}_4\text{O}_2$: 178.0491, found: 178.0490.

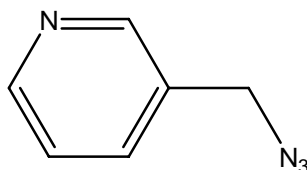
4-(Azidomethyl)pyridine (13)



The reaction was performed with dry conditions under Argon. 4-Pyridylcarbinol (0.22 g, 2 mmol) was weighed in a 25 mL round bottomed flask and diphenyl phosphorazide (0.66 g, 2.4 mmol) was added via a syringe. Dry toluene (4 mL) was added via a syringe. The mixture was put on an ice bath. DBU (0.37 g, 2.4 mmol) was added via a syringe. The mixture stirred for 2 hours at 0°C , and then for another 20 hours at room temperature.

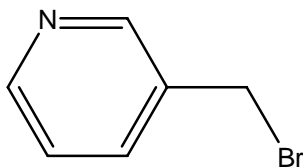
EtOAc (1 mL) was added and the mixture was extracted with toluene (3 x 7 mL), the organic phase was evaporated under reduced pressure. A white crystalline powder was obtained, but it was insoluble in all available deuterated solvents, hence no NMR results were obtained. The experiment was aborted.

3-(Azidomethyl)pyridine (14)



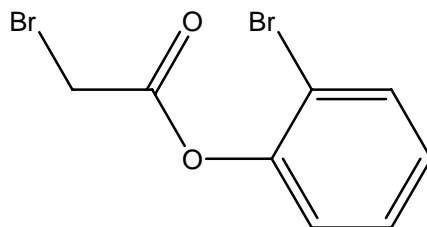
The reaction was performed with dry conditions under Argon. 3-Pyridylcarbinol (1.09 g, 10 mmol) was weighed in a 100 mL round bottomed flask and diphenyl phosphorazide (3.30 g, 12 mmol) was added via a syringe. Dry toluene (18 mL) was added via a syringe. The mixture was put on an ice bath. DBU (1.83 g, 12 mmol) was added via a syringe. The mixture stirred for 4 hours at 0°C, and then for another 20 hours at room temperature. The mixture was washed with water first, and then with HCl. This procedure resulted in 3 phases. The experiment was aborted.

3-(Bromomethyl)pyridine (15)



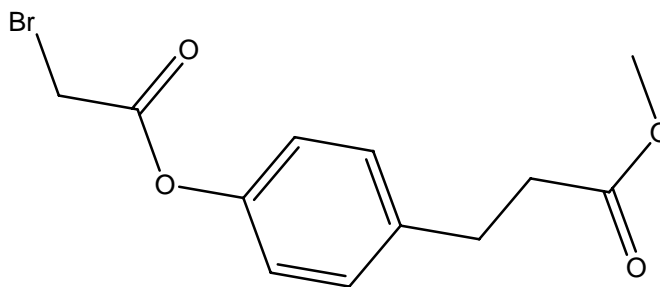
3-(Bromomethyl-)pyridine hydrobromide (0.52 g, 2 mmol) was weighed in a 25 mL round bottomed flask and EtOH:H₂O, 1:1 (4 mL) was added. The mixture was allowed to stir at room temperature. NaOH (1 M) was added until the pH reached 8. The mixture stirred over night. A white precipitate was observed, but extraction with EtOAc did not succeed and the experiment was aborted.

2-Bromophenyl 2-bromoacetate (16)



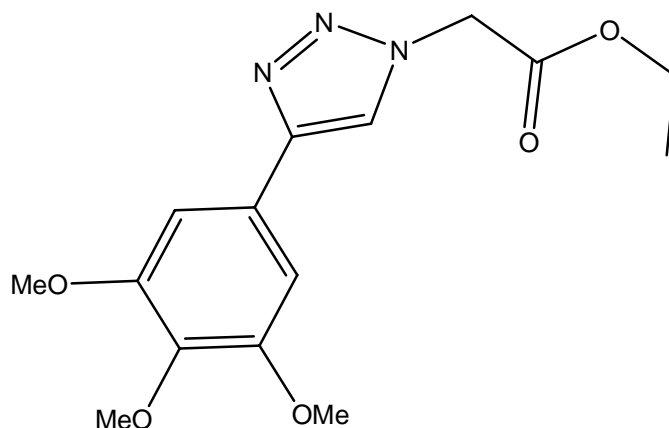
The reaction was performed according to the general procedure for bromides. Chemicals and amounts used: Bromoacetylchloride (1.73 g, 11 mmol), 2-bromophenol (1.73 g, 10 mmol), triethylamine (1.11 g, 11 mmol) and dichloromethane (20 mL). The reaction furnished 0.87 g (30%) as a colorless liquid. R_f 0.60 (hexane:EtOAc, 3:1); ^1H NMR (CDCl_3 , 300 MHz) δ 7.62 (d, J 7.8 Hz, 1H) 7.35 (t, J 8.1 Hz, 1H) 7.18-7.13 (m, 2H) 4.37 (s, 2H) ; ^{13}C NMR (CDCl_3 , 75 MHz) δ 164.96, 147.62, 133.44 ppm, 128.59, 127.85, 123.31, 115.71, 25.05.

Methyl 3-(4-(2-bromoacetoxy)phenyl)propanoate (17)



The reaction was performed according to the general procedure for bromides. Chemicals and amounts used: Bromoacetylchloride (1.73 g, 11 mmol), methyl 3-(4-hydroxyphenyl)propanoate (1.80 g, 10 mmol), triethylamine (1.11 g, 11 mmol) and dichloromethane (20 mL). The reaction furnished 0.72 g (24%) as a white solid. Mp; 54-55°C; R_f 0.38 (hexane:EtOAc, 3:1); ^1H NMR (CDCl_3 , 300 MHz) δ 7.23 (d, J 8.7 Hz, 2H) 7.05 (d, J 8.7 Hz, 2H) 4.27 (s, 2H), 3.67 (s, 3H), 2.96 (t, J 8.1 Hz, 2H), 2.63 (t, J 7.8 Hz, 2H) ; ^{13}C NMR (CDCl_3 , 75 MHz) δ 173.06, 165.91, 148.71, 138.71, 129.41, 121.07, 51.65, 40.85, 35.52, 30.25.

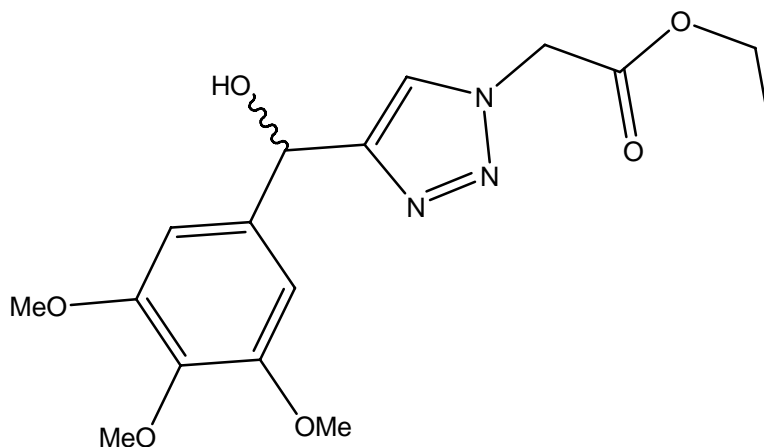
Ethyl 2-(4-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-1-yl)acetate (18)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

Ethyl 2-bromoacetate (167 mg, 1 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (65 mg, 1.05 mmol), 5-ethynyl-1,2,3-trimethoxystilbene (192 mg, 1mmol), sodium ascorbate (20 mg, 0.1 mmol) and copper sulphate (13 mg, 0.05 mmol). TLC showed that the reaction was not completed. Sodium azide (38 mg, 0.5 mmol), sodium ascorbate (10 mg, 0.05 mmol) and copper sulphate (7 mg, 0.025 mmol) were added. The mixture was allowed to stir over night. The reaction mixture was diluted with ice-water and EtOAc (20 mL) was added. The organic phase was washed 3 times with saturated ammonium chloride solution (10 mL). The organic phase was dried (MgSO₄) and filtered. The solvent was evaporated under reduced pressure, furnishing 165 mg (total yield 52%) as slightly yellow colored crystals. Mp: 95-97°C; R_f 0.66 (Hexane:EtOAc, 1:10); ¹H NMR (CDCl₃, 300MHz); δ 7.90 (s, 1H), 7.06 (s, 2H), 5.20 (s, 2H), 4.29 (q, *J* 7.8 Hz, 2H), 3.92 (s, 6H), 3.87 (s, 3H), 1.31 (t, *J* 7.8 Hz, 3H); ¹³C NMR (CDCl₃, 300MHz); δ 166.27, 153.62, 138.24, 125.84, 120.77, 103.04, 62.50, 60.92, 56.24, 50.97, 14.06. A peak for the second triazole carbon was not found in the spectrum. HRMS calc for C₁₅H₁₉N₃O₅: 321.1325, found; 321.1330.

Ethyl 2-(4-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (19)

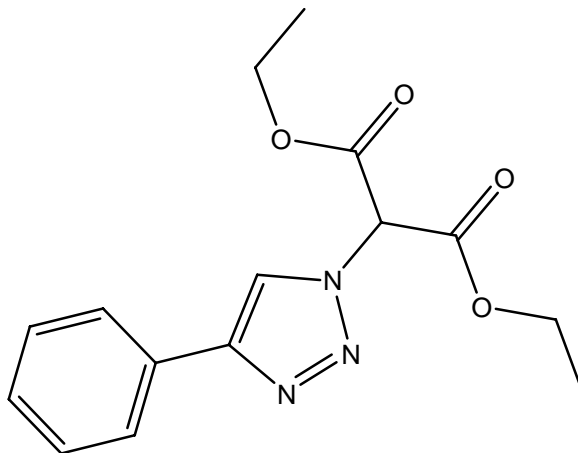


The reaction was performed as outlined in general procedure for one-pot click reactions.

The chemicals used and the data is described below.

Ethyl 2-bromoacetate (668 mg, 4 mmol), t-BuOH:H₂O solution (1:1, 16 mL), sodium azide (260 mg, 4.2 mmol), 1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (889 mg, 4 mmol), sodium ascorbate (79 mg, 0.4 mmol) and copper sulphate (50 mg, 0.2 mmol). The mixture was diluted with ice water and washed with saturated ammonium chloride solution (3 x 30 mL). The mixture was extracted with dichloromethane (2 x 50 mL), the organic phase was dried (MgSO₄) and evaporated under reduced pressure. NMR data showed that only starting materials were isolated.

Diethyl 2-(4-phenyl-1H-1,2,3-triazol-1-yl)malonate (20)

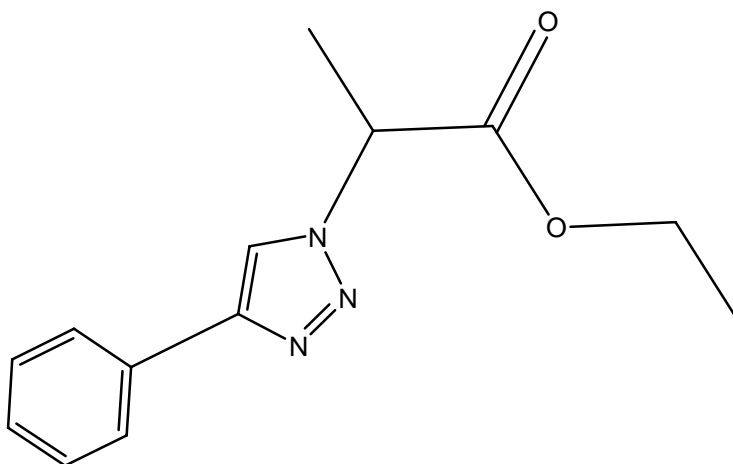


The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

Diethyl 2-bromomalonate (476 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (137 mg, 2.1 mmol), phenylacetylene (204 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). The mixture was diluted with ice-water and washed with saturated ammonium chloride solution (3 x 15 mL). The mixture was extracted with EtOAc (3 x 20 mL).

The organic phase was dried (MgSO₄) and filtered. The solvent was evaporated under reduced pressure, a yellow liquid was obtained. NMR data showed that the product was not pure.

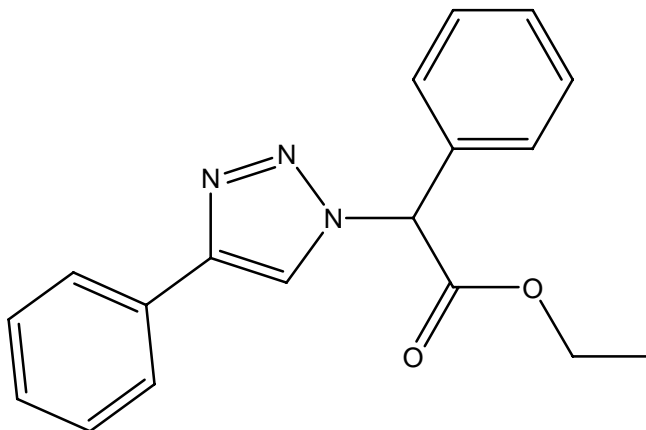
Ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (21)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

Ethyl-2-bromopropionate (362 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (137 mg, 2.1 mmol), phenylacetylene (204 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). The mixture was diluted with ice-water and washed with saturated ammonium chloride solution (3 x 15 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic phase was dried (MgSO₄) and filtered. The solvent was evaporated under reduced pressure, a green liquid was obtained. NMR data showed that the product was not pure.

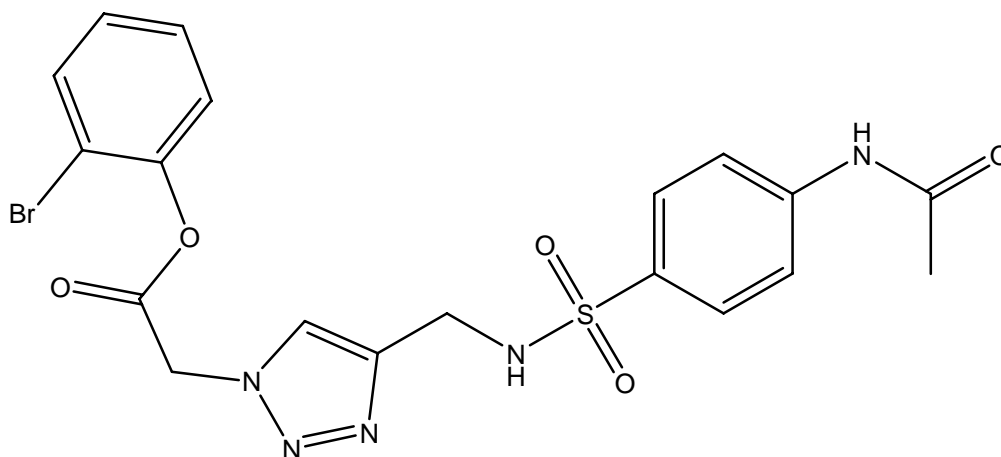
Ethyl 2-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (22)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

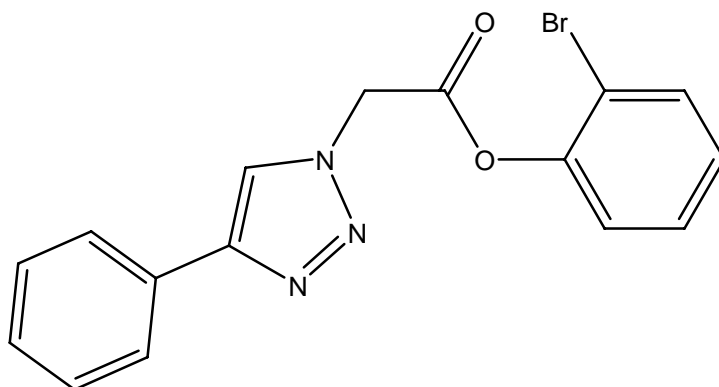
Ethyl bromphenylacetate (486 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (137 mg, 2.1 mmol), phenylacetylene (204 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). The mixture was diluted with ice-water and washed with saturated ammonium chloride solution (3 x 15 mL). The mixture was extracted with EtOAc (3 x 20 mL). The organic phase was dried (MgSO₄) and filtered. The solvent was evaporated under reduced pressure, a green liquid was obtained. NMR data showed that the product was not pure.

2-Bromophenyl 2-(4-((4-acetamidophenylsulfonamido)methyl)-1H-1,2,3-triazol-1-yl)acetate (23)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below. Chemicals: 2-Bromophenyl 2-bromoacetate (294 mg, 1 mmol), t-BuOH:H₂O solution (1:1, 2 mL), sodium azide (68 mg, 1.05 mmol), *N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (252 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol) and copper sulphate (12 mg, 0.05 mmol). The mixture was diluted with ice-water and washed with saturated ammonium chloride solution (3 x 10 mL). The mixture was extracted with EtOAc (3 x 15 mL). The organic phase was dried (MgSO₄) and filtered. NMR data showed that no product was isolated.

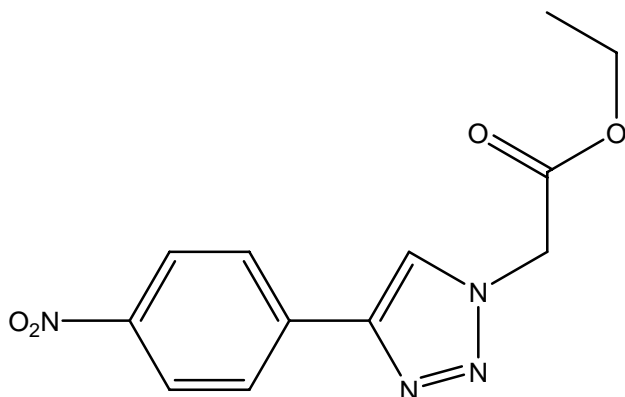
2-Bromophenyl 2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetate (24)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below. Chemicals: 2-Bromophenyl 2-bromoacetate (294 mg, 1 mmol), t-BuOH:H₂O solution (1:1, 2 mL), sodium azide (68

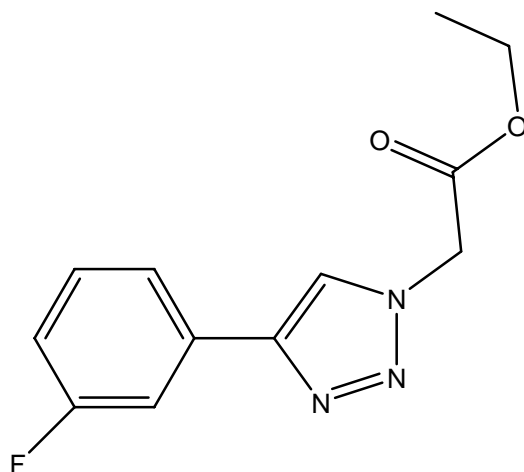
mg, 1.05 mmol), phenylacetylene (102 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol) and copper sulphate (12 mg, 0.05 mmol). The mixture was diluted with ice-water and washed with saturated ammonium chloride solution (3 x 10 mL). The mixture was extracted with EtOAc (3 x 15 mL). TLC showed that no product was formed, and the experiment was aborted.

Ethyl 2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)acetate (25)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below. Ethyl bromoacetate (332 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (137 mg, 2.1 mmol), 1-ethynyl-4-nitrobenzene (97%, 303 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). Total yield 292 mg (53%); mp 144-145°C; R_f 0.66 (Hexane:EtOAc 1:4); ¹H NMR (DMSO, 300 MHz) δ 8.85 (s, 1H), 8.32 (d, *J* 9.0 Hz, 2H), 8.14 (d, *J* 9.0 Hz, 2H), 5.52 (s, 2H), 4.21 (q, *J* 7.2 Hz, 2H), 1.24 (t, *J* 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.98, 146.59, 144.38, 136.79, 128.33, 125.94, 124.23, 61.58, 50.63, 13.89.

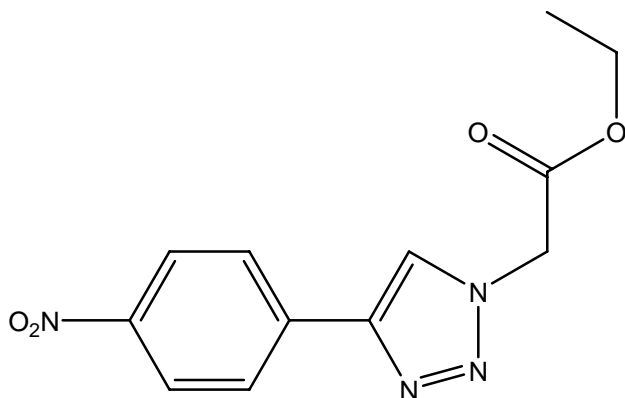
Ethyl 2-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)acetate (26)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

Ethyl bromoacetate (332 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (137 mg, 2.1 mmol), 1-ethynyl-3-fluorobenzene (98%, 245 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). Total yield 209 mg (42%) as a slightly green solid; Mp: over 250°C; *R*_f 0.72 (hexane:EtOAc, 1:4); ¹H NMR (DMSO, 300 MHz) δ 8.68 (s, 1H), 7.72-7.14 (m, 4H), 5.47 (s, 2H), 4.20 (q, *J* 7.2 Hz, 2H), 1.04 (t, *J* 7.2 Hz, 3H); HRMS calcd. for: C₁₂H₁₂FN₃O₂ [*M*⁺]: 249.0914, found: 249.0913.

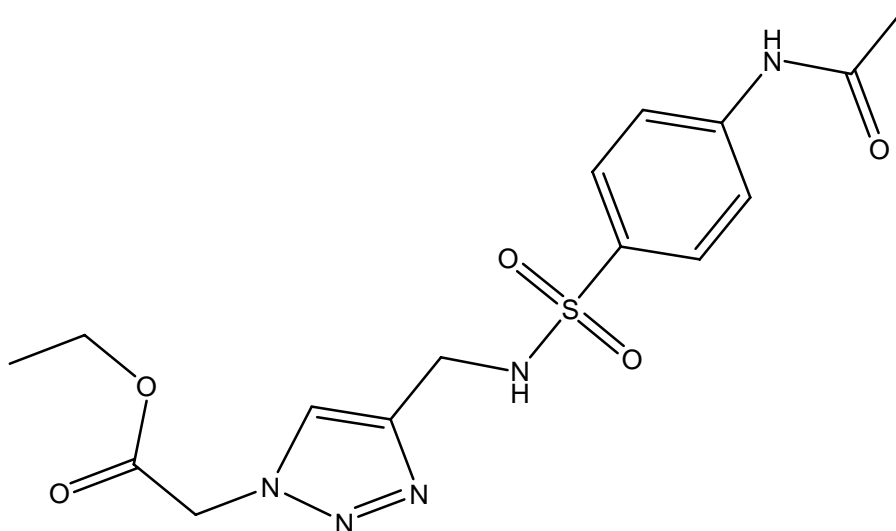
Ethyl 2-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)acetate (25)



The reaction was performed as outlined in general procedure for one-pot click reactions, at a temperature of 40°C. The chemicals used and the data is described below. Ethyl

bromoacetate (664 mg, 4 mmol), t-BuOH:H₂O solution (1:1, 8 mL), sodium azide (273 mg, 4.2 mmol), 1-ethynyl-4-nitrobenzene (97%, 606 mg, 4 mmol), sodium ascorbate (80 mg, 0.4 mmol) and copper sulphate (50 mg, 0.2 mmol). Total yield 961 mg (87%); mp 144-145°C; R_f 0.66 (Hexane:EtOAc 1:4); ¹H NMR (DMSO, 300 MHz) δ 8.85 (s, 1H), 8.32 (d, *J* 9.0 Hz, 2H), 8.14 (d, *J* 9.0 Hz, 2H), 5.52 (s, 2H), 4.21 (q, *J* 7.2 Hz, 2H), 1.24 (t, *J* 7.2 Hz, 3H); ¹³C NMR (DMSO, 75 MHz) δ 166.98, 146.59, 144.38, 136.79, 128.33, 125.94, 124.23, 61.58, 50.63, 13.89..

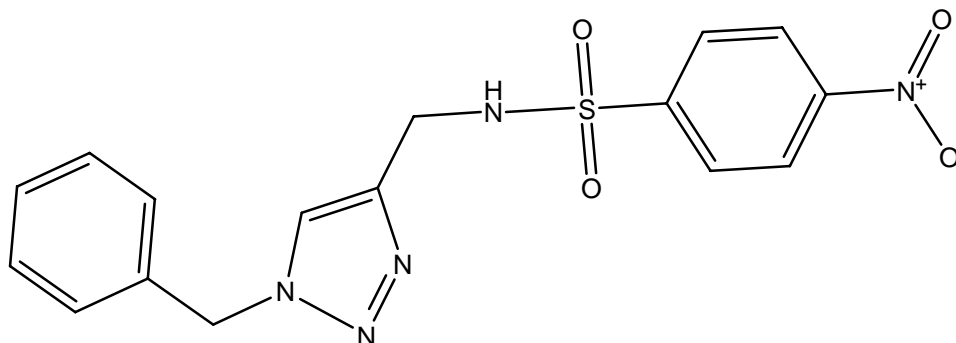
Ethyl 2-(4-((4-acetamidophenyl)sulfonamido)methyl)-1H-pyrazol-1-yl)acetate (28)



The reaction was performed as outlined in general procedure for one-pot click reactions. The chemicals used and the data is described below.

Ethyl bromoacetate (166 mg, 1 mmol), t-BuOH:H₂O solution (1:1, 4 mL), sodium azide (68 mg, 1.05 mmol), *N*-(4-(*N*-prop-2-ynylsulfamoyl)phenyl)acetamide (252 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol) and copper sulphate (13 mg, 0.05 mmol). Total yield 221 mg (88%); mp 176-178°C; ¹H NMR (DMSO, 300 MHz) δ 10.31 (s, 1H), 8.03 (s, 1H), 7.92 (s, 1H), 7.80-7.65 (m, 4H), 5.32 (s, 2H), 4.17 (q, *J* 7.1 Hz, 2H), 4.03 (s, 2H), 2.09 (s, 3H), 1.22 (t, *J* 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.87, 167.07, 142.67, 133.82, 127.64, 124.61, 118.48, 61.35, 50.17, 38.60, 24.04, 13.88; HRMS calcd. for C₁₅H₁₉N₅O₅S [M⁺]: 381.1107, found: 381.1074.

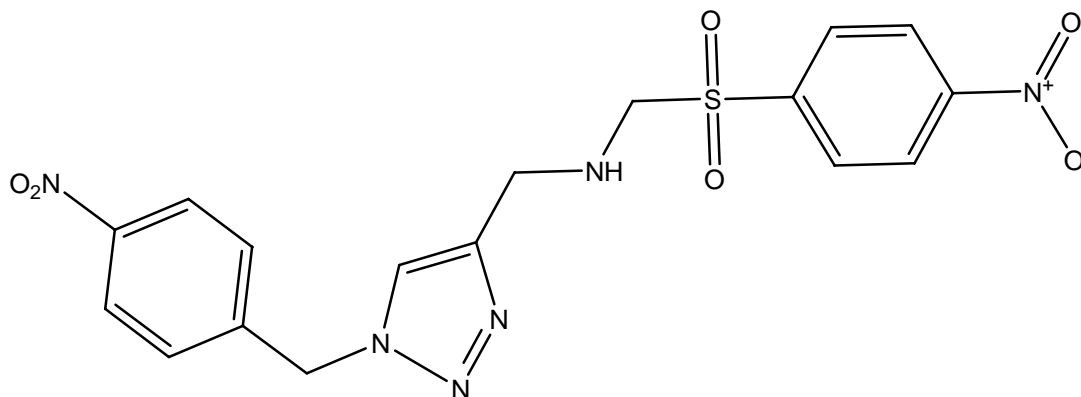
***N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-nitrobenzenesulfonamide (29)**



The reaction was performed as outlined in general procedure for click reactions. The chemicals used and the data is described below.

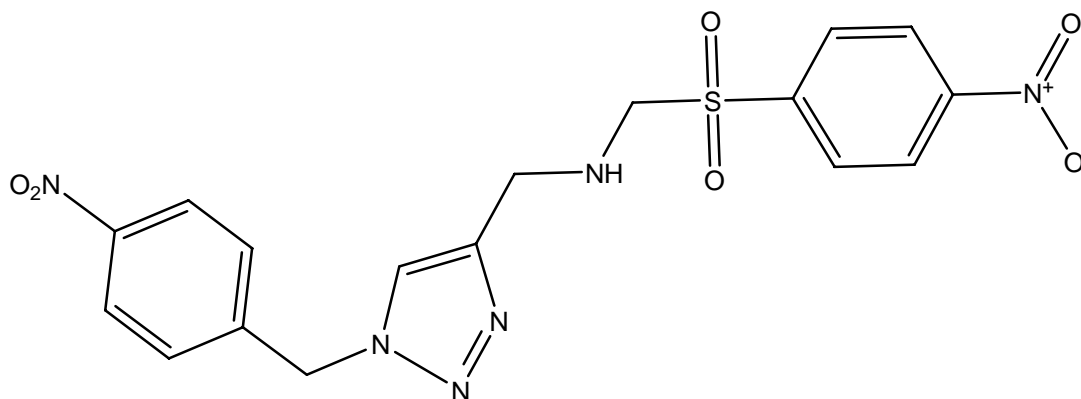
(Azidomethyl)benzene (266 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), 4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (509 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). A total yield 572 mg (77%) as a yellow solid. *R*_f 0.56 (hexane:EtOAc (1:4); mp 157-158°C; ¹H NMR (DMSO, 300 MHz) δ 8.53 (s, 1H), 8.31 (d, *J* 9.0 Hz, 2H), 7.97 (d, *J* 9.0 Hz, 2H), 7.90 (s, 1H), 7.35-7.22 (m, 5H), 5.49 (s, 2H), 4.14 (s, 2H); ¹³C NMR (DMSO, 75 MHz) δ 149.32, 146.10, 135.80, 128.58, 128.06, 127.99, 127.83, 124.29, 123.34, 52.59, 37.83.

1-(1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)-*N*-((4-nitrophenylsulfonyl)methyl)methanamine (30)



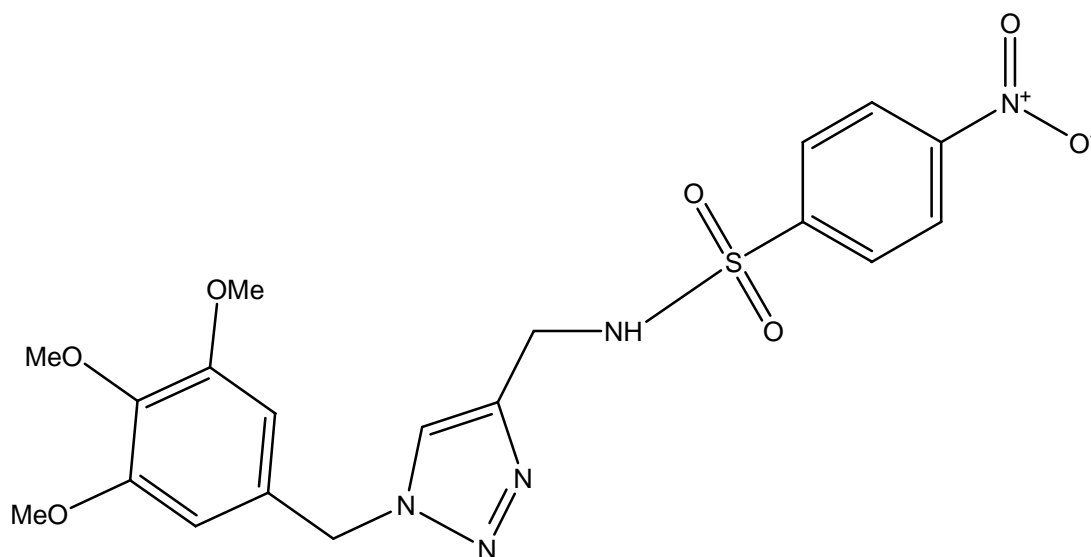
The reaction was performed as outlined in general procedure for click reactions. The chemicals used and the data is described below. Chemicals: 1-(Azidomethyl)-4-nitrobenzene 356 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 4 mL), 4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (509 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). The reaction provided a poor yield and TLC showed that the product was impure.

1-(1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)-*N*-((4-nitrophenylsulfonyl)methyl)methanamine (30)



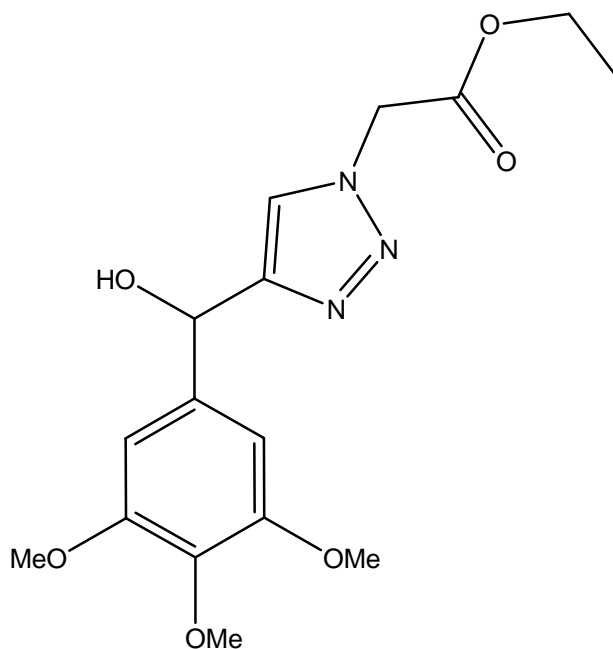
The reaction was performed as outlined in general procedure for click reactions. The chemicals used and the data is described below. Chemicals: 1-(Azidomethyl)-4-nitrobenzene 356 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 8 mL), 4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (509 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol). A total yield 572 mg (77%) as a yellow solid. *R*_f 0.36 (hexane:EtOAc, 1:4); mp 183-185°C; ¹H NMR (DMSO, 300 MHz) δ 8.58 (s, 1H), 8.31 (d, *J* 8.7 Hz, 2H), 8.22 (d, *J* 9.0 Hz, 2H), 7.99 (d, *J* 8.4 Hz, 3H), 7.47 (d, *J* 8.7 Hz, 2H), 5.69 (s, 2H), 4.17 (s, 2H); ¹³C NMR (DMSO, 75 MHz) δ 149.26, 147.11, 146.08, 143.15, 128.88, 127.97, 124.26, 123.70, 58.91, 37.82.

4-Nitro-*N*-((1-(3,4,5-trimethoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (31)



H₂O (20 mL), 4-nitrobenzene-1-sulfonyl chloride (492 mg, 2 mmol) and propargylamine (112 mg, 2 mmol) was mixed in 250 mL round bottomed flask. The pH was set to 8 with Na₂CO₃. 5-(Azidomethyl)-1,2,3-trimethoxybenzene (442 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol), EtOH (20 mL) and copper sulphate (25 mg, 0.1 mmol) was added. The mixture was allowed to stir over night. Ice water was added and a precipitate formed. The precipitate was filtered off and washed with ammonium solution (5%, 3 x 25 mL) and cold diethyl ether (3 x 25 mL), furnishing a white solid total yield 400 mg (43%). R_f; 0.32 (hexane:EtOAc, 1:4); mp 148-152°C; ¹H NMR (DMSO, 300 MHz) δ 8.5 (s, 1H), 8.34 (d, *J* 9.0 Hz, 2H), 8.00 (d, *J* 9.0 Hz, 3H), 6.67 (s, 2H), 5.41 (s, 2H), 4.12 (s, 2H), 3.75 (s, 6H), 3.63 (s, 3H); ¹³C NMR (DMSO, 75 MHz) δ 152.90, 149.39, 145.95, 143.20, 137.26, 131.18, 128.04, 124.31, 123.30, 59.88, 55.84, 52.81, 37.20;

Ethyl 2-(4-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-1H-1,2,3-triazol-1-yl)acetate (32)



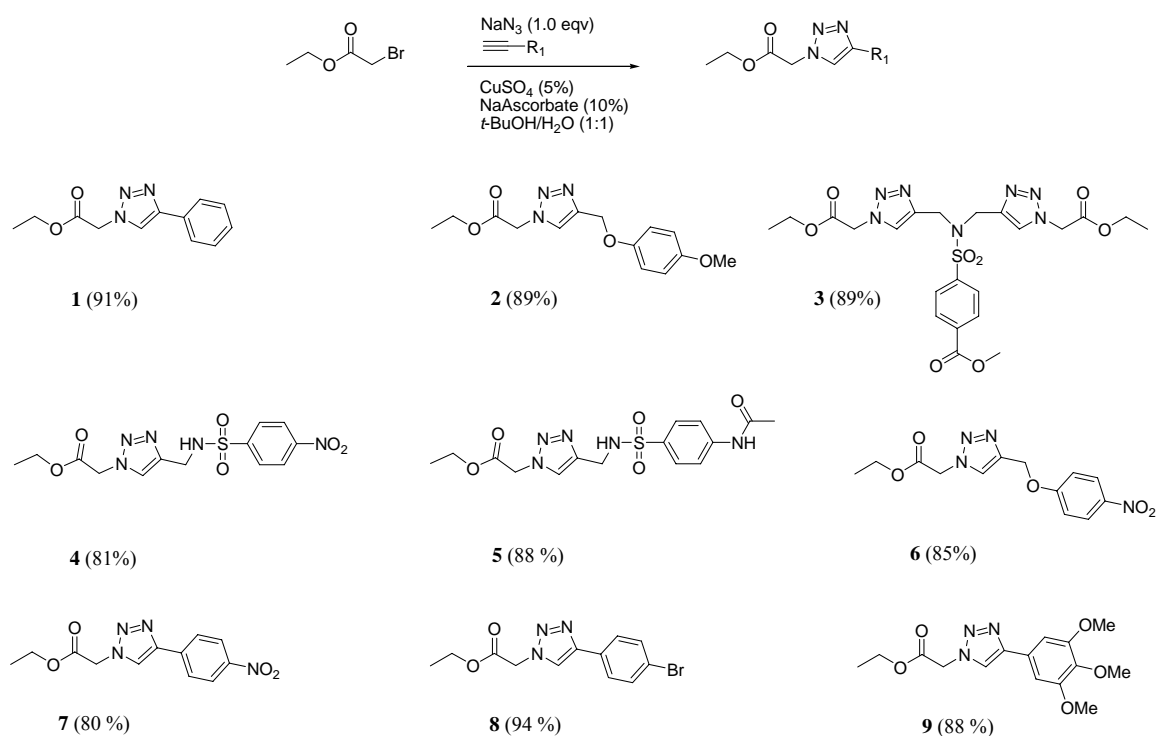
The reaction was performed as outlined in general procedure for click reactions. The chemicals used and the data is described below. Ethyl 2-azidoacetate (259 mg, 2 mmol), t-BuOH:H₂O solution (1:1, 8 mL), 1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (445 mg, 2 mmol), sodium ascorbate (40 mg, 0.2 mmol) and copper sulphate (25 mg, 0.1 mmol).

4 Further studies and conclusion

4.1 Further studies

In order to obtain antibacterial activity for the prepared sulfonamides **28**, **29**, **30** and **31**, hydrolysis of the amide group or reduction of the nitro group needs to be done. Due to time limits, these two reactions were not performed. This chemistry should be possible to do with established methods. In preliminary studies, hydrolysis of sulfonamide **9** in basic aqueous conditions afforded the desired sulfonamide product. However, this sulfonamide was difficult to obtain without sodium chloride as a contaminant, and further studies should be done in order to obtain libraries of pure sulfonamides.

This one-pot methodology was employed for a wide range of substituted terminal alkynes in our group as depicted in Scheme 1.³²



Scheme 1

4.2 Conclusion

A one-pot procedure for the direct conversion of α -halo esters to 1,2,3-triazoles has been developed. These reactions were efficiently performed in neutral aqueous solutions (pH=7-8) at ambient temperature. Molar equivalents of the halide, sodium azide and alkyne are employed in this mild 1,3-dipolar cycloaddition reaction. The method circumvents the problems encountered with the isolation of organic azides, and complements other recently published methods for the preparation of 1,2,3-triazoles.³³⁻³⁵ The operational simplicity of this method makes it attractive for preparative applications as well as for the synthesis of screening libraries for drug discovery.

This method should be useful for preparation of libraries of biologically active compounds, for example for sulfonamides such as **7**, **8** and **9**. Furthermore, the advantages of the guiding principles of click chemistry, as exemplified for the Cu(I)-catalyzed cycloaddition between azides and terminal alkynes, has been used for the preparation of several new 1,4-disubstituted 1,2,3-triazoles.

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